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THE ILEUM: FUNCTION, RESECTION, AND BYPASS

L. Beaty Pemberton

In the past fifteen years, many investigators have realized that the ileum performs functions not shared by the remainder of the small bowel. The three basic functions of the ileum are the absorption of bile salts and cholesterol, the absorption of vitamin B_{12} and the regulations of small intestinal motility and emptying by the ileocecal valve. This recent knowledge has provided a better understanding of abnormalities which occur with ileal disease or resection. The purpose of this review is to provide an understanding of the physiology of the ileum and to discuss application of these physiologic principles to some well-known clinical situations.

ABSORPTION OF BILE SALTS AND CHOLESTEROL

The ileum is the main site of bile salt absorption. Weiner studied the *in vivo* absorption of conjugated bile salts from various levels of the guinea pig small intestine. He demonstrated that regardless of bile salt concentration, the main absorptive site was the ileum. In addition, this investigator showed that ileectomy in dogs caused excessive bile salt loss.[1] In man, Borgstrom confirmed that conjugated bile salts were absorbed mainly in the distal small bowel.[2]

Conjugated bile salts are transported by the ileum into the portal blood and are cleared by the liver. The liver then excretes them into the bile ducts and then into the small intestine. They travel down the intestine and are finally reabsorbed in the ileum. This cycle is known as the enterohepatic circulation of bile salts.[3]

The total amount of bile salt in the enterohepatic circulation is normally about 4 gms. This bile salt pool recirculates six to eight times per day, which means that the intestine receives about 24 to 32 gms. of bile salts per day to aid in the absorption of fats. The liver synthesizes about 300 mg. of bile salt per day—enough to replace fecal losses and maintain pool size. About five per cent of the bile salt pool per day is not absorbed by the ileum and is excreted in the stool.[4]

Bile salts have the structure of a detergent with a lipid soluble steroid nucleus and a water soluble polar tail composed of taurine or glycine. In aqueous solutions, such as that within the intestinal lumen, they form molecular aggregates or micelles with the non-polar ends clustered inward and the polar tails facing outward.[3] In 1962, Hofmann and Borgstrom confirmed that conjugated bile salts formed micelles in human small intestinal fluid. The concentration of bile salts within the intestinal lumen must be above the "critical micellar concentration" to form micelles. Under normal circumstances, the rapidly recirculating bile salt pool maintains a concentration well above this critical point.[5]

The absorption of ingested fat by the normal adult is almost complete, which

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means that 95 to 98 per cent is digested and absorbed. Most fat in the diet consists of neutral fats or triglycerides Triglycerides are made from two building blocks: glycerol and fatty acids. One molecule of glycerol and one fatty acid are combined to form a monoglyceride. The addition of two more fatty acids to the remaining hydroxyl groups on the glycerol forms a triglyceride. The triglycerides in the average diet are insoluble in water. In the aqueous solution of the small intestine, bile salts emulsify the triglycerides and disperse this fat into small droplets. Since pancreatic lipase acts only at the interface between fat and water, the emulsification of triglyceride by bile salts provides a maximum surface upon which lipase may act. At the lipid-water interface, pancreatic lipase, which accounts for 95 per cent of fat digestion, hydrolyses the small globules of triglyceride to monoglyceride and free fatty acid which readily enter the bile salt micelles.[3]

The micelles then transport these products of lipolysis to the mucosal cell for absorption. Although the exact mechanism of fat transport into the mucosal cell remains obscure, the bile salt micelles containing monoglyceride and fatty acids become adherent to the intestinal cell membrane. Here they somehow deliver their lipid to the mucosal cell and reenter the intestinal lumen without being absorbed themselves.[6]

Even though some fat can be absorbed directly without the aid of micelles, micelle formation is a major pathway of fat absorption. Certain lipids such as vitamins A, D, K, and cholesterol are dependent on this micellar solubilization for absorption. Bile salts, but not pancreatic lipase, are essential for the absorption of these substances. This observation may explain why patients with isolated pancreatic insufficiency do not become deficient in vitamins A, D, and K.[7]

Whenever the ileum is damaged by disease or is lost by resection or bypass, diarrhea and steatorrhea will occur. In this syndrome, the enterohepatic circulation is interrupted and bile salt absorption from the ileum is decreased. When bile salts cannot be reabsorbed from the ileum, the bile salt pool decreases, which lowers the concentration of bile salts in the proximal small intestine. Fat absorption is impaired and steatorrhea results. Moreover, since hepatic bile salt synthesis is increased in the face of impaired bile salt absorption, more bile salts than normal reach the colon in spite of the fact that the overall bile salt pool is decreased. Since bile salts in the large bowel act as cathartics by inhibiting water absorption and altering motility, the increased fecal content of bile salts accounts in large part for the diarrhea. Hofmann has referred to this loss of a functioning ileum as the syndrome of ileal disease and the broken enterohepatic circulation.[8]

Finally, although cholesterol can be absorbed throughout the small intestine, its main site of absorption is the ileum. The small intestine receives daily 0.5 gm. of cholesterol from the diet and 1 to 3 gms. of endogenous cholesterol, mainly from bile. This cholesterol is mostly absorbed from the ileum by passive diffusion into the lymphatic system. Bile salts are essential for its absorption of cholesterol.[9] Siperstein has demonstrated an enterohepatic cholesterol cycle which depends on this preferential ileal absorption of cholesterol.[10] Thus, the ileum is the principal site for bile salt and cholesterol absorption in the intestine.

VITAMIN B_{12} ABSORPTION

The ileum is the major site for the absorption of vitamin B_{12}. This vitamin is abundant in the normal diet. Absorption of vitamin B_{12} depends on its combining, in the stomach, with intrinsic factor, a mucoprotein from the gastric fundus. This B_{12}-intrinsic factor complex then passes through the intestine and is selectively absorbed in the terminal ileum either by facilitated diffusion or by pinocytosis. Since in man only minute amounts of vitamin B_{12} are absorbed by other parts of the bowel, loss of the ileum eliminates vitamin B_{12} absorption and produces vitamin B_{12} deficiency. Inasmuch

as the liver stores this vitamin in large amounts, the deficiency does not manifest itself for one to four years. Thus, vitamin B_{12} deficiency is a late sequela of ileal resection or disease.[11]

ILEOCECAL VALVE

An important part of the ileum is the ileocecal valve. The ileocecal valve, which is a physiological rather than an anatomical sphincter, maintains a downward gradient of pressure from ileum to cecum. When cecal pressure is less than ileal, the valve intermittently discharges small spurts of intestinal contents into the cecum. Conversely, distention and increased cecal pressure closes the sphincteric mechanism preventing regurgitation into the ileum. Since loss of extrinsic innervation does not alter its function, intrinsic nerves regulate the ileocecal valve, which is usually closed. By delaying movement of chyme into the colon, the ileocecal valve slows forward motility and transit time, and thus allows food a longer time to remain in contact with the absorptive surface of the small bowel.[12]

Abnormalities which occur after surgical extirpation of the small bowel emphasize the importance of the ileocecal valve. Its removal shortens small bowel transit time, which impairs efficiency of the absorptive processes. In dogs with distal small bowel resection and an intact ileocecal valve, Kremen demonstrated that further resection or exclusion of the valve invariably produced increases in fecal fat excretion and further weight loss.[13] In patients with similar small bowel resections, Kalser reported that those with resection of the ileocecal valve had three times as much fecal fat loss and more fecal water loss than those with an intact valve.[14] Thus, loss of the ileocecal valve is an important factor in malabsorption after massive small bowel resection or exclusion.

ILEAL RESECTION

Humans have a large amount of functional small bowel reserve. Limited resections, involving less than 50 per cent of the small bowel rarely produce nutritional difficulties or diarrhea. Patients with more extensive resections, involving 50 to 80 per cent of the small intestine, undergo an initial period of adjustment to the altered physiological state, but most eventually do well with dietary management alone. In contrast, massive resections involving more than 80 per cent of small bowel present extremely difficult problems. About 25 per cent of these patients become totally incapacitated as a result of such procedures. Removal of the jejunum and ileum and reestablishment of continuity with a duodenocolonic anastomosis is incompatible with life.[15] Rarely, patients with 6 to 18 inches of small bowel below the ligament of Treitz have survived for periods greater than three years.[16,17]

Since the ileum has its specific functions, ileal resection produces more serious problems than jejunal resection. Ileal resection alone eliminates the three primary functions of the ileum. First, the enterohepatic circulation is interrupted, which produces diarrhea and steatorrhea.[18] Secondly, absence of the ileocecal valve produces rapid transit and decreased absorption. Finally, loss of the ileum virtually eliminates absorption of vitamin B_{12} and eventually produces deficiency of this vitamin. Investigators have observed all of these abnormalities, both in experimental animals and in man after ileal resection.

Kremen studied the differential effects of jejunal and ileal resection in dogs. From his studies, he concluded that resection of the proximal 50 to 70 per cent of the small bowel produces minimal ill-effects. Weight is maintained, and the absorption of protein and fat is not significantly reduced. In contrast, loss of the distal half of small intestine produces a marked reduction in fat absorption with increased fat in the stool and weight loss. Presence of the ileocecal valve improved nutritional adjustment much more after distal than after proximal small bowel resection. Although dogs undergoing ileal resection with an intact ileocecal valve showed weight loss and increased fat in the stool, subsequent

resection of the ileocecal valve markedly increased weight loss in these animals. In summary then, the presence or absence of the ileum and ileocecal valve significantly influenced the nutritional adjustment of dogs after resection of the small bowel.[13]

Kalser followed the course of 25 patients after small bowel resection of varying degrees. He concluded that loss of the ileum, rather than removal of the ileocecal valve or jejunum, causes steatorrhea and weight loss. In six of these patients who underwent resection of the ileocecal valve plus only one to two feet of ileum, fecal fat remained near the normal value of 5.0 gms. or less per day. Thus, removal of the ileocecal valve is not the basic cause of steatorrhea. Similarly, steatorrhea did not correlate with small bowel motility. Normal motility and transit time may be present in patients with steatorrhea as shown by six of Kalser's patients who had reasonably normal motility studies after complete ileal resection, and daily excreted 20 gms. of fecal fat. In contrast, length of remaining ileum correlated well with the amount of steatorrhea. After resections leaving approximately five feet of small bowel, six patients with more ileum than jejunum excreted 11.6 gms. of fat per day, compared to 42.8 gms. per day in 12 patients with only jejunum. The loss of ileum, then, is the primary cause of steatorrhea following small bowel resection, and the more ileum removed, the more severe the steatorrhea.[14]

Kalser also found nutritional abnormalities in these patients who underwent various resections. Severe megaloblastic anemia due to vitamin B_{12} deficiency developed in 5 out of 14 patients 18 months to 5½ years after ileal resections. Secondly, increased water loss with dehydration occurs after removal of the ileocecal valve and/or large segments of the colon. Patients without an ileocecal valve had six times greater fecal water loss than patients with similar lengths of resections, but with intact ileocecal valves. Since the colon adapted to intestinal resection by increasing its absorption of water, a generous length of remaining colon significantly decreased problems of water loss. Finally, although patients exhibited decreases in serum albumin, prothrombin, calcium, and cholesterol, these deficiencies responded readily to therapy and did not pose any real problem.[14]

With a meaningful understanding of the physiology of the ileum, physicians can better anticipate and manage nutritional abnormalities occurring after small bowel resection. Furthermore, the surgeon should be aware that when a choice is possible, retention of the ileum and ileocecal valve will minimize the postoperative nutritional problems.

ILEAL BYPASS FOR HYPERCHOLESTEROLEMIA

The use of ileal bypass to reduce serum cholesterol is based on the rationale that the ileum is the main site of cholesterol and bile salt absorption. Removal of the ileum from the fecal stream markedly decreases absorption of both endogenous and exogenous cholesterol. Furthermore, bypass of the ileum eliminates the primary site of bile salt absorption in the small bowel which interrupts enterohepatic circulation of bile salt with a corresponding decrease in the bile salt pool. Since cholesterol is the precursor for bile salt synthesis, the stimulation of hepatic production of bile salts by decreasing the bile salt pool constitutes a metabolic drain from the endogenous cholesterol pool.

Thus, ileal bypass lowers body and serum cholesterol by decreasing intestinal absorption, increasing the fecal loss of cholesterol and bile salts, and accelerating hepatic conversion of cholesterol to bile salts.

By anastomosing the proximal ileum to the ascending colon, Buchwald and Varco excluded the distal 200 cm. or one-third of the small intestine as treatment for hypercholesterolemia in 19 patients. These patients were placed on a low cholesterol diet for three months prior to surgery. One year after bypass, the average reduction of serum choles-

terol was 40 per cent with one-half of the patients maintaining serum cholesterols below 200 mg. per 100 ml. Although the effect of lowered cholesterol on existing arteriosclerosis was difficult to evaluate, there was subjective improvement in patients with angina pectoris and objective regression of subcutaneous xanthomas. In addition, while patients with ileal bypass exhibited initial steatorrhea and diarrhea, which was sometimes quite marked, these symptoms improved after about three months. By then, most patients produced one to three stools per day and maintained normal weights. These patients did not display any nutritional deficiencies. Routinely, however, they were given parenteral vitamin B_{12}. [19]

Laboratory experiments strongly suggest that ileal bypass lowers serum cholesterol and protects animals from developing serious atherosclerosis. Younger performed ileal bypass on dogs rendered hypothyroid with radioactive iodine. On 20 per cent cholesterol diets, dogs with ileal bypass and hypothyroidism alone developed an average cholesterol of 286 mg. per 100 ml., while animals with hypothyroidism alone developed an average cholesterol of 792 mg. per 100 ml. At autopsy about a year after the initial procedures, dogs in the control group (no surgery) had severe atherosclerosis, while those animals with ileal bypass had minimal or no atheromatous changes.[20]

Buchwald demonstrated the protective effects of ileal bypass in rabbits receiving high cholesterol diets. Rabbits with bypass had average cholesterols of 80 mg. per 100 ml. compared to 1000 mg. for control animals. Autopsy studies of rabbits with ileal bypass showed minimal atherosclerosis, while control animals had marked atheromatous changes.[21]

Although the above experimental data seem encouraging, results from animal experiments may not be applicable to man, and clinical trials of ileal bypass have been disappointing. Buchwald reported reduction in serum cholesterol in all 19 patients who underwent ileal bypass. In 16 of these patients with known coronary disease, two patients developed myocardial infarction in the immediate postoperative period and two others had a coronary thrombosis 5 and 25 months respectively after surgery. Coronary and femoral arteriography failed to reveal objective regression of atheromatous disease.[19] Although lowered serum cholesterol appears to stop progression of atheromata, regression or disappearance of intimal plaques has not been observed or documented. Perhaps, ileal bypass may be of more value if performed early for hypercholesterolemia before the atheromatous process has advanced.

SMALL INTESTINAL BYPASS FOR OBESITY

Small intestinal bypass for obesity decreases fat absorption and produces steatorrhea and weight loss. Fat absorption is impaired both by loss of absorptive surface and by lack of bile salts. By eliminating the major site of bile salt absorption, ileal bypass produces the syndrome of the broken enterohepatic circulation with diarrhea, reduction of bile salt pool, steatorrhea, and weight loss. When intestinal bypass significantly alters fat digestion and absorption, the short length of intestine that remains in contact with ingested food has often produced malabsorption of water, vitamins, and electrolytes. This drawback is one of the major arguments against performing this procedure to treat obesity.

Some characteristics of clinical intestinal bypass are illustrated by a study of 11 patients who underwent jejunocolic anastomoses using variable lengths of jejunum beyond the ligament of Treitz. Shibata found that the shortest segments (15 inches) of jejunum produced the largest excretion of fecal fat, while the longest segments (25 inches) caused much less increase in fecal fat. In all cases, weight loss was proportional to fecal fat excretion. After one year, weight loss based on preoperative weight was approximately 50 per cent for the patients with shorter lengths of retained

jejunum and 25 per cent for those with the longer segments.[22]

Some other parameters of digestive function in these 11 patients were markedly abnormal in the early postoperative period, but returned toward normal after six to twelve months. All patients showed an initial decrease in serum albumin which was readily corrected with a high protein diet in all but one individual. Diarrhea to a marked degree occurred in the early postoperative period, but became stable with approximately three stools per day after six months. Xylose tests to measure carbohydrate absorption were abnormal at six, but normal at 12 months. One death occurred from hepatitis, which produced a mortality rate of 9 per cent.[22]

Although the above study of Shibata describes some typical results of small bowel bypass for obesity, other reports indicate some serious complications that may follow these procedures. A significant complication of intestinal bypass is fatty degeneration of the liver and hepatic failure. Bondar reported fatty livers in two of seven patients who underwent bypass. After re-establishing intestinal continuity, these livers returned to normal.[23]

To investigate this problem of fatty livers in dogs, Bondar compared the effects of massive small intestinal bypass to a similar loss of small bowel by resection. After massive resection, two dogs survived with no evidence of fatty livers. After exhibiting diarrhea and weight loss for three months, these animals adjusted with mushy stools and a stable weight, which was 75 per cent of its preoperative value. In contrast, after massive bypass, all eight dogs showed fatty degeneration of the liver and six animals died as a result of the metabolic consequences of the procedure. The two survivors showed progressive deterioration with increasing signs of liver failure. Bondar could find no obvious cause for the difference between dogs with massive resections who lived and those with a comparable bypass who died. Although the defunctionalised loop contained no abnormal bacterial flora, these experimental animals were unable to adapt to intestinal bypass.[23]

Payne[24] described two out of ten patients who developed fatty livers after jejunocolic bypass and Maxwell reported two patients with marked fatty livers, one with jejunoileal and the other with jejunocolic bypass. Although the cause of fatty degeneration of the liver is obscure, Maxwell theorized that choline deficiency, which produces fatty livers in pancreatic insufficiency and alcoholism, might result from altered intestinal bacteria that could convert dietary choline into its inactive form of trimethylamine.[25] Although other factors are probably needed to explain this phenomenon, fatty degeneration of the liver is one of the significant risks involved in performing intestinal bypass for obesity.

Another significant complication is malabsorption of calcium and magnesium. DeMuth reported a fatal case of hypocalcemic and hypomagnesemic tetany after small intestinal bypass.[26] The explanation of these low serum levels is that steatorrhea causes malabsorption of vitamin D, calcium, and magnesium. In spite of impaired fat absorption, pancreatic lipase continues to break down dietary fat within the intestinal lumen. Both calcium and magnesium readily combine with free fatty acids to produce insoluble soaps which are excreted in the stool. Formation of insoluble soaps impairs absorption and lowers the serum values of calcium and magnesium. To combat this malabsorptive problem, the patient may be given enough calcium carbonate pills to supply calcium for both insoluble soaps and intestinal absorption.

A third problem of intestinal bypass is excessive diarrhea with dehydration and electrolyte imbalance. Loss of water and electrolytes in the stool can be markedly decreased by preserving a large amount of colon in the fecal stream and by binding free fatty acids and bile salts. These latter substances, which result from the bypass, are cathartics and produce diarrhea. As above, treatment with calcium carbonate, up to 20 gm.

per day, will precipitate fatty acids and bile salts as insoluble soaps and thus inactivate them. This treatment will often change the character of the stools from watery diarrhea to about three semisolid stools per day, which greatly decrease water and electrolyte losses.

Fourthly, intestinal bypass decreases absorption of fat-soluble vitamins A, D, and K and virtually eliminates absorption of vitamin B_{12}. To compensate for impaired absorption, oral vitamin supplements can supply increased amounts of fat-soluble vitamins. However, since the bypass procedure removes most of the ileum from the food stream, vitamin B_{12} should be supplied parenterally.

Although an effective procedure for producing weight loss, small intestinal bypass for obesity does involve significant morbidity and some mortality. The bypass procedure must produce severe metabolic derangement in order to produce weight loss. At present, most investigators do not recommend this operation as a routine treatment for obesity, but suggest that it be reserved for treating extreme obesity with imminent life-threatening complications.[22-26]

On the other hand, small bowel bypass might become a complementary measure to help patients lose weight and to maintain the loss on a low calorie diet. Morgan reported a patient weighing 458 pounds who received jejunoileal bypass with 15 inches of jejunum and 10 inches of terminal ileum including the ileocecal valve. After a year, this patient was able to maintain a stable weight of 210 pounds on a normal diet. Apparently, this more conservative bypass provided a good compromise between excessive fat absorption and disabling diarrhea. Although most of the small bowel was excluded, presence of the ileocecal valve and right colon greatly decreased problems with water and electrolytes. Fecal loss of calcium, magnesium, and potassium was not excessive. Excretion of ingested fat was 5 per cent before and 40 to 50 per cent after bypass.[28]

At present, the jejunoileal bypass as an experimental procedure is recommended for treating patients with extreme obesity, while jejunocolic shunt should not be used. From 11 patients undergoing jejunocolic bypass, Lewis reported four patients with satisfactory results, six patients requiring repeated hospitalization for electrolyte deficiencies, and one postoperative death. Two patients with chronic fatigue requested another operation to restore intestinal continuity.[29] Moreover, Payne states that patients with jejunocolic shunts often develop dehydration from intractable diarrhea, electrolyte abnormalities, abdominal pain, and liver failure. He recommends the elimination of jejunocolic shunts for the control of obesity.[24]

In contrast, Payne reported 70 patients who underwent jejunoileal shunts with few complications but with three postoperative deaths. He found that an intestinal shunt with 14 inches of jejunum and 4 inches of ileum induced progressive weight loss to a maintenance level of near normal body weight. Most problems after these jejunoileal shunts, such as electrolyte depletion, diarrhea, fatigue, and flatulence were easily managed with diet and drugs. Most patients adjusted easily to the shunt and were satisfied with the results. Only one patient had intestinal continuity restored because of degenerating liver function. Although Payne considers jejunoileal bypass to be an investigative procedure requiring further research, this more conservative shunt appears to be a useful surgical approach to the patient with extreme obesity.[30]

SUMMARY

The ileum has been discussed in regard to its function, resection, and bypass for hypercholesterolemia and obesity. The functions of the ileum involve absorption of bile salts and cholesterol, absorption of vitamin B_{12}, and regulation of small bowel motility by the ileocecal valve. Since these functions are not shared by the remainder of the small intestine, ileal resection poses greater problems than jejunal resection. Bypass of the ileum lowers serum cholesterol, but its

objective benefits for the patient are difficult to document. Although it remains an experimental procedure, jejunoileal shunts have been used successfully for the treatment of extreme obesity. The ileum is an important part of the small intestine that warrants our continued interest.

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PHYSIOLOGY REVIEW: URINARY TRACT OBSTRUCTION

William C. DeWolf

Urinary tract obstruction is a phenomenon which is familiar to all physicians, yet poorly understood by many. To understand its symptomatology one must first gain a basic appreciation of the physiology involved. It is the purpose of this paper to review this briefly and assess its pathologic significance.

The urine drainage system begins with the minor calyces surrounding the renal papillae and ends at the urethral meatus. Component parts consist of minor calyces, major calyces, renal pelvis, ureter, urinary bladder, and urethra. The only function of the conduit system is to conduct urine from the kidney to the outside in the most efficient way possible. The force for this movement is provided not only by gravity, but also by the muscular bundles which surround this system. Rhythmic contractions occur which force the urine from the kidney to the bladder, which has a capacity of several hundred milliliters and thus represents a reservoir in the system. Filling occurs slowly and, generally speaking, without sensation whereas emptying occurs relatively quickly and is initiated by a conscious effort. Once bladder emptying has begun, it usually is sustained until complete. The structure and function of this relatively direct system is changed in urinary tract obstruction. The hallmark of such obstruction is dilatation of the urinary tract proximal to the site of involvement.

Obstruction of the kidney is different from obstruction of other secretive organs in that its function continues. Obstruction of a salivary gland, for instance, results in a non-functioning atrophied gland. When the kidney is obstructed, however, urine formation is slowed but does not stop altogether. The urine, which is blocked from its normal route of excretion, is resorbed regardless of whether the obstruction is partial or complete. The peculiar relationship between urine formation and urine disposal accounts for the phenomenon of hydronephrosis.

Urine Formation

Glomerular filtration represents the initial step in urine formation. Each normal human glomerulus filters approximately .00006 ml of fluid per minute from the blood flowing through its capillaries; the normal kidneys in man contain approximately two million nephrons. Therefore the total glomerular filtrate is about 120 ml/minute or 170 liters/day. The actual mechanics of filtration depends on a pressure gradient between the glomerular capillary lumen and the lumen of Bowman's capsule. The process is purely mechanical and does not rely on cellular transport mechanisms. The capillary hydrostatic pressure (100 cm H_2O) must exceed the capillary colloid oncotic pressure (33 cm H_2O) plus tubular resistance (33 cm H_2O). The resultant filtration pressure of the glomerulus then is around 34 cm H_2O. Logically, then, if the proximal tubule hydrostatic pressure were increased to a critical level (as occurs during obstruction), the glomerular

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filtration rate (GFR) would decrease. This is, indeed, the case as found both clinically and experimentally.

Urine Disposal

As mentioned previously, hydronephrosis is formed because of an imbalance in urine formation and excretion. If the normal urinary tract is blocked, then there must be another route of excretion (or resorption) somewhere along the urinary pathway; otherwise the pressure within the conducting structures would rise rapidly until glomerular filtration ceased, in which case progressive dilatation of hydronephrosis would not occur but rather primary atrophy would intervene.

Evidence for such resorption is multiple and demonstrates a constant turnover of fluid within the renal pelvis. It is found that, as obstruction proceeds with time, there is an increase in intrapelvic glucose and chloride concentration and a decrease in urea concentration. Outflow can be demonstrated by placing a dye in the renal pelvis and noting its progressive disappearance after a few days.

There are several possible sites for resorption of fluid.[1] *Pyelovenous* backflow is quantitatively the most important route of resorption in acute hydronephrosis. Experimental evidence points to the fornix of the minor calyx with its underlying venous plexus as the site for urine resorption. A pressure of 100 to 130 cm H_2O is needed to initiate pyelovenous backflow. Once begun, and resorptive pathways are formed, the process can be maintained at much lower pressures of approximately 80 cm H_2O (Fig. 1). Steroids sometimes decrease the hydronephrotic change accompaning acute urinary obstruction—perhaps owing to a decreased inflammatory response such that the routes of backflow through pyelovenous channels are not closed by fibrosis. Usually after approximately two weeks of obstruction there is gradual dilatation of the fornices and thickening of the pelvic and papillary epithelium. The interstitial spaces become filled with new connective tissue and pyelovenous backflow ceases.

Tubular backflow then becomes more important. During early ureteral obstruction the intrapelvic hydrostatic pressure compresses the papillary tissues, thus compressing the collecting ducts and preventing tubular backflow; as hydronephrosis advances, however, the intrapelvic hydrostatic pressure is decreased

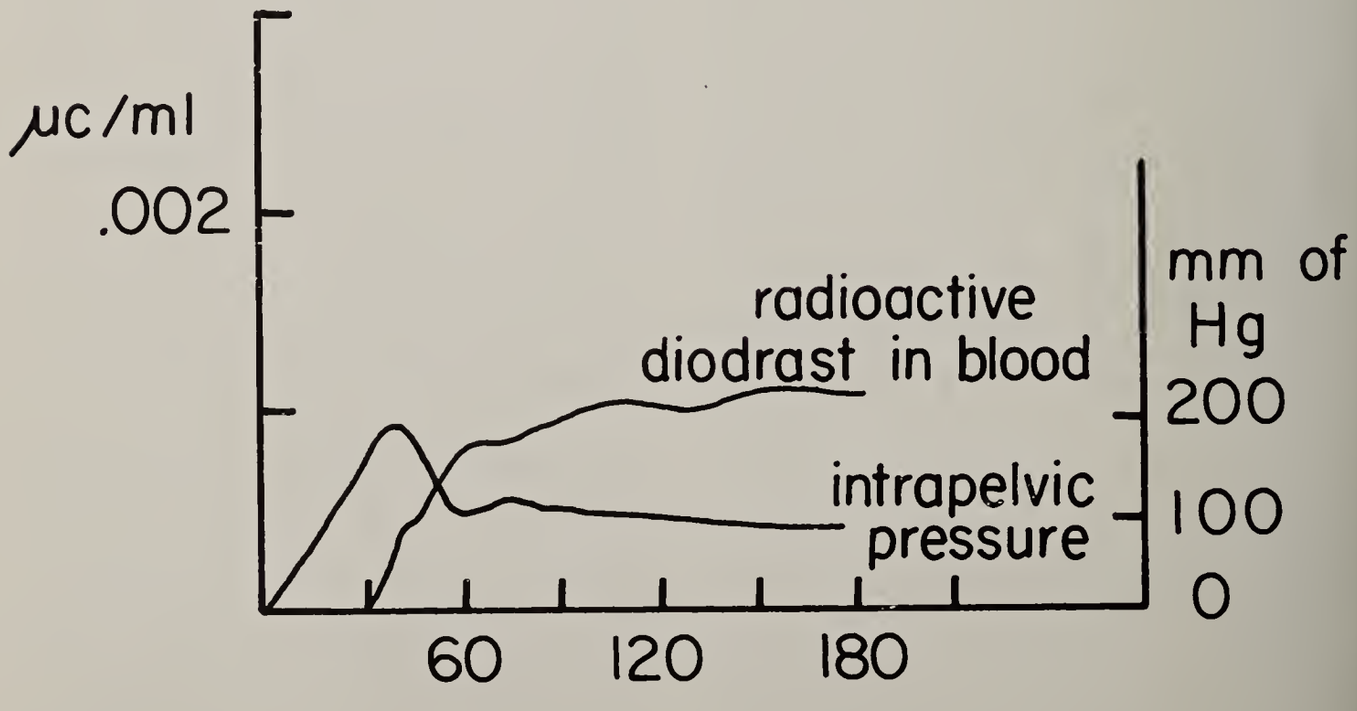

Fig. 1

and radial distention of the pelvis occurs. The net effect is to open the ducts and allow tubular backflow.[2] The actual mechanism whereby urine is resorbed into the blood stream is not exactly known. It is to be understood that tubulovenous backflow does not necessitate urine flow back into the tubules, but rather urine may be resorbed directly from the tubules when intratubular pressure equals intrapelvic pressure.

Acute *vs.* Chronic Obstruction

After understanding the basic mechanism for high urinary tract obstruction we can now consider some of its consequences. Following acute obstruction with attendant transmission of increased pressure to the tubules, there will be a decrease in filtration gradient between the glomerular capillaries and Bowman's space, and the glomerular filtration rate in the involved nephrons will fall. The entry of salt and water into the nephrons will then be decreased. In acute obstruction the active proximal tubular reabsorption of sodium with its water is still intact. Under these circumstances of decreased glomerular filtration rate, and thus decreased tubular flow, a proportionally greater amount of sodium and water will be reabsorbed than found in normal glomerular filtrate. In addition, urine osmolality will be increased because, again, of the proportionally greater amount of water reabsorbed, this time in relation to nonsodium solute in the urine. In acute obstruction, then, there is an underperfusion of the distal nephron which results in a decrease in sodium concentration (especially during water diuresis), a decrease in urine output, and an increase in urine osmolality as compared to a normal kidney. These findings are not unique to acute obstruction but occur in any case of diminished glomerular filtration rate per nephron (assuming that the tubules are normal) and are identical to the findings in unilateral renal artery stenosis.[3]

The chronically obstructed kidney behaves quite differently from the kidney with acute obstruction. Experimental evidence indicates that, as in acute obstruction, the total glomerular filtration rate is reduced. However, in chronic obstruction a *larger* fraction of both filtered salt and water are excreted than in normal kidneys. This pattern is quite similar to that found in chronic parenchymal renal disease. The drop in glomerular filtration rate appears in the face of an even greater drop in nephron population thus suggesting a state of hyperfiltration per functioning nephron. This elevated glomerular filtration rate per nephron, plus a diminished fractional reabsorption of filtrate in the proximal nephron results in a marked *over*perfusion of the distal nephron. The larger volume of fluid delivered to each distal nephron results not only in greater C_{H_2O} per 100 ml glomerular filtrate, but also in a *higher* rate of sodium excretion and a *lower* urine osmolality during water diuresis than found in normal kidneys. There is a decrease in absolute rate of C_{H_2O} because of a diminution in the total number of functioning nephrons.

The concentrating ability of the kidney in the face of persisting urinary tract obstruction has not been well studied. However, data on the behavior of kidneys following release of acute obstruction are available. Animals acutely obstructed for brief periods of time elaborate urine of lower osmolality than that of controls. In addition, chemical analyses of renal medullary sections from these animals indicate a decreased concentration of urea and sodium.[4] An explanation is as follows: renal blood flow is *increased* following acute intermittent obstruction.[5] This is associated with a decrease in para-amino-hippuric acid extraction during renal plasma flow measurements. Evidence thus favors a greater fraction of total renal blood flow traversing noncortical (or medullary) circulation. It appears then that there is an increase in vasa recta blood flow which diminishes the hypertonicity of the medulla by "wash out." The result is an impairment in concentrating ability. It should be mentioned that chronic obstruction produces a decrease in renal blood flow by approxi-

mately 40 per cent. This is partly due to vascular compression by the progressing hydronephrosis. The decrease in renal blood flow is associated with a decrease in glomerular filtration. One would thus expect that with a decrease in urine formation the hydronephrosis would be less. This, however, is not true. The progress of hydronephrosis is linked closely with the nutrition of the parenchyma, and with decreased blood supply to the cortex there is more rapid parenchymal degeneration, with an increase in hydronephrotic dilatation. The longer the obstruction persists, the less the chances of return of renal function. Usually after 30 days, return of function is minimal, although cases have been reported in which function has returned after four months.[6]

Obstruction of one kidney causes compensatory hypertrophy of the contralateral kidney just as occurs after unilateral nephrectomy. The source of the stimulus for hypertrophy is not yet known. The hypertrophy that is noted is mainly the result of tubular enlargement. The nephrons do not increase in number, but the cells of the tubules undergo hyperplasia which begins 24 to 48 hours after unilateral nephrectomy (rat).[7] In addition, glomeruli increase in size, and blood vessels increase in diameter. This process is essentially complete at 20 days in experimental animals.

The functional characteristics of a compensated kidney are somewhat different from those of a normal one. The glomerular filtration rate is not as great as that of two kidneys but the tubular excretion rate can actually exceed normal. This merely reinforces the idea that, histologically, renal compensation consists more of tubular than glomerular hyperplasia. The diameter of the renal artery of such compensated unilateral human kidneys is increased by an average of 12.5 per cent which allows almost double the volume of blood to flow to the kidney. The calculated renal plasma flow is likewise almost double (88 per cent).[8]

Laboratory assessment of the patient with obstructive nephropathy can best be made with blood urea nitrogen (BUN) and serum creatinine levels. The normal BUN:creatinine ratio is 10:1. This ratio is increased with gastrointestinal bleeding, which raises the BUN (through reabsorption of proteins through the intestine), and is decreased sometimes in liver disease. Because of impairment in urea synthesis, patients with renal disease secondary to obstructive uropathy also have an increase in BUN as compared to serum creatinine levels.[9] The cause relates to the mechanism by which each of these substances is excreted. Creatinine is eliminated principally by glomerular filtration with 28 per cent being secreted by renal tubules. Urea, although filtered at approximately the same rate as creatinine, undergoes tubular reabsorption because it is a smaller and more diffusible molecule. The amount that is reabsorbed is dependent upon the urine flow rate; the greater the flow rate, the smaller amount absorbed. Likewise, the greater the obstruction, the lesser the glomerular filtration rate; thus there is less flow and more urea reabsorbed (Fig. 2). When the flow of urine is 2 cc or more per minute, approximately 35 per cent of filtered urea is reabsorbed. Abnormal BUN creatinine ratio of similar character is seen in cases of impaired renal blood flow which, again, results in decreased urine flow through the tubules. However, in this case the cause is from decreased glomerular filtration rate rather than increased hydrostatic back pressure.

The Ureter

The response of the ureter to obstruction is fairly uniform regardless of etiology. If acutely blocked, as in calculus disease, the ureter will react with hyperperistalsis and local vascular spasm. Chronic obstruction stimulates muscular hypertrophy in an effort to force urine past the obstruction. This results in elongation and tortuosity of the ureter. Oftentimes additional fibrous bands develop along the course of the ureter which further angulates it, sometimes to the point

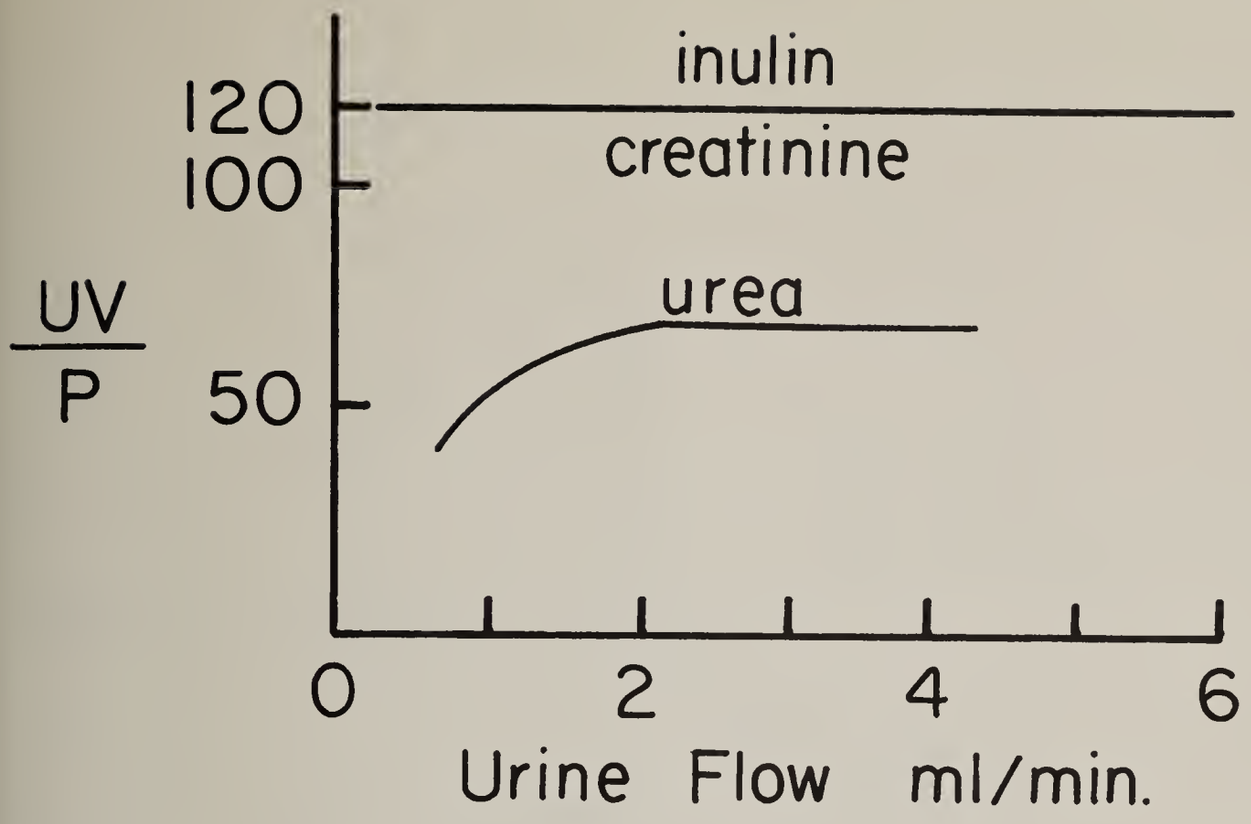

Fig. 2

that secondary stenosis may develop. At this stage, surgical removal of the obstruction may not prevent renal destruction. If the obstruction is not relieved in time the ureteral wall becomes so attenuated that it loses its contractile power and enters in the phase of decompensation whereby hydroureter results. High ureteral obstruction results in earlier caliectasis and hydronephrosis than low ureteral obstruction, not only because there is less ureter to absorb the increase in back pressure on the kidney, but also because there is less surface area for ureteral lymphatics to carry off urine.

Trigonal hypertrophy is a newly recognized cause of ureteral obstruction and is important in understanding the obstructive nephrophy which may follow bladder outlet obstruction.[10] The anatomical arrangement of the intravesical-trigone complex is so designed that contraction of the longitudinal muscles of the extravesical ureter and the intravesical ureter in opposite directions stretches the ureter over the ureteral meatus in the bladder wall thus compressing the roof against the floor and the entire ureter laterally against the supporting muscles within the wall of the bladder (Fig. 3). This action is under control of the sympathetic nervous system which allows it to behave as a distinct unit separate from the bladder (which is innervated by the parasympathetic nervous system). Continuation of the ureteral musculature into the trigone is an important feature in closure of the intravesical ureter during voiding, for it is here that the ureter is "anchored" during ureteral contraction. Interruption of this muscle disrupts the trigonal mechanism and leads to decreased resistance to urine flow into and out of the bladder at the ureterovesical junction. The result is ureteral reflux. Conversely it should be true, then, that hypertrophy of the trigone (as occurs in detrusor hypertrophy following bladder outlet obstruction) should put an increased stretch on the valve mechanism of the ureter and cause increased resistance to the flow of urine past the ureterovesical junction into the bladder. Experimentation has found this to be true. The implications of this low ureteral obstruction secondary to bladder outlet obstruction are great. Renal back pressure has always been accepted as a sequel of bladder outlet obstruction. Rest-

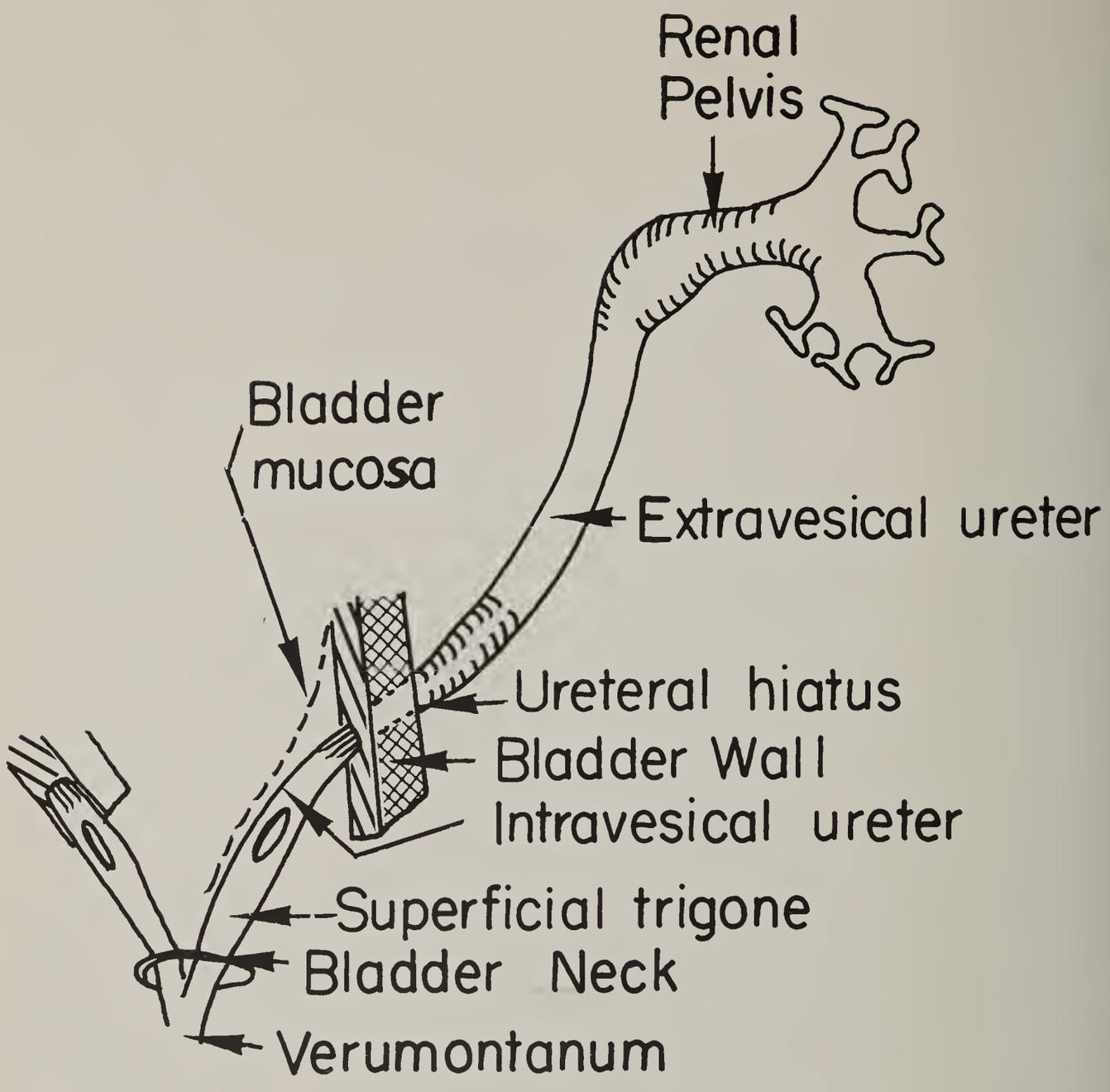

Fig 3

ing intravesical pressure in such obstructed bladders is near normal (20 to 30 cm H_2O); therefore in chronic bladder outlet obstruction, back pressure on the kidneys can hardly be caused by high intravesical pressure assuming there is little or no reflux (the incidence of reflux in such cases is quite low—between 5 and 10 per cent). It has been shown that with bladder distention the trigone is subjected to a considerable amount of stretch and that the stretching increases the resistance to flow through the intravesical ureter without increasing the intravesical pressure. Therefore draining a chronically distended bladder improves renal function not by relieving high intravesical pressure, which is not present, but rather by relieving the trigonal muscle from constant stretch. This leads to diminished resistance to flow through the intravesical ureter and improved urinary drainage.

Obstruction below the Bladder

Bladder outlet obstruction is first met by changes in bladder function. Like the heart, the bladder is an organ which receives fluid and forcefully expels it. Similarly, under conditions of increased work load, the bladder enters into a phase of compensation followed by decompensation.

Resistance to voiding is increased with distal obstruction. The bladder compensates for this by muscular hypertrophy, the thickness of the bladder wall sometime doubling. Normal intravesical voiding pressures are in the range of 30 to 40 cm H_2O; however, under circumstances of muscular hypertrophy, pressures may reach 100 cm H_2O or more. Hypertrophy of the bladder musculature reveals itself as trabeculation along the mucosal wall from the hypertrophied muscular bands. The trigonal muscles, which normally are minimally discernible, also respond by hypertrophy thus becoming a prominent ridge within the bladder.

Occasionally reflux may occur. In bladder outlet obstruction, as well as in neuromuscular dysfunction, the area lying just above the ureteral hiatus is altered by formation of cellules and diverticula which upset the normal backwall support of the ureter and the antireflux mechanism. The final effects, then, of outlet obstruction upon the ureterovesical junction can be either partial ureteral obstruction or reflux.

Physiologic Explanation of Symptoms for Bladder Outlet Obstruction

In the early phases of distal obstruction, as mentioned previously, the bladder musculature hypertrophies. The urinary stream is normal because the outlet obstruction is balanced by increased voiding pressure. As hypertrophy continues the detrusor muscle becomes hyperirritable. If the bladder becomes distended the urge to void is felt. In a normal individual this urge is repressed. However, in a patient with a hypertrophied detrusor, the contraction is extremely strong and the bladder may even go into spasm. Thus symptoms of *urgency* and *frequency* with nocturia are produced. As the bladder continues to hypertrophy the patient notices *hesitancy* in initiating urination due to the time needed for the bladder to develop contractions strong enough to overcome resistance to obstruction. At this point the contraction phase may not last long enough for all the urine to be expelled, and exhaustion of the muscle occurs prematurely. After a short interval the detrusor is again able to contract and the patient then notices *intermittency* of urination.

As obstructional resistance exceeds detrusor power, the contractions of the bladder become ineffective in completely expelling the contents of the bladder, and residual urine collects. This represents the early phase of bladder decompensation. If outlet obstruction increases, there becomes a progressive imbalance between ability to expel urine and resistance such that more and more urine remains in the bladder. Symptoms, especially frequency, become more marked. If the bladder becomes over-stretched with more than 1000 cc of urine, it then loses its capacity to contract, and overflow incontinence ensues. Occasionally acute decompensation may occur after a rapid filling, such as is found after acute alcholic ingestion.

Sequellae of Obstruction

Urinary tract obstruction produces stasis which has two important long-term consequences—*infection* and *calculus formation*. Hydronephrosis can lead to pyonephrosis which represents an end stage of renal disease. Likewise both infection and obstruction can result in calculus formation which completes a vicious cycle—each promoting and possibly resulting from the other.

Summary

Urinary tract obstruction involves a wide range of disease processes. An outline of the basic physiology of each anatomical unit of the urinary tract has been presented and its obstructive pathophysiology detailed.

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ABSTRACTS

OF PUBLICATIONS BY THE STAFF

ALLERGY

Aronson SB, Sassetti R: Experimental ocular hypersensitivity to polyepinephrine and its analogues. *Invest Ophthal 9:12, 1970.*

Experimental hypersensitivity to epinephrine and to some of its analogues was induced in the rabbit. These changes included chemosis, limbal hyperemia, subepithelial corneal infiltrates, and anterior chamber cells and flare; changes already described in human epinephrine hypersensitivity. Positive skin reactions and circulating antibody were recorded after systemic immunization to polyepinephrine; only skin sensitivity occurred in polyaldomet immunization. This experimental model closely simulates epinephrine hypersensitivity as seen in man.

Hyde JS, Buranskul B, Vithanasai V: Effect of cromolyn sodium on childhood asthma. *Ann Allerg 28:449-458, 1970*

Double-blind assessments were found to coincide with definite improvement using cromolyn sodium (CS) treatment in 11 of 15 asthmatic children on corticosteroids and 22 of 42 in a non-corticosteroid group. Four patients were much better on placebo. The effect of CS treatment was significant ($p < 0.01$) for the non-corticosteroid treated group and highly significant ($p < 0.001$) for the total group. For 12 of 17 children changes in moderate and marked airway obstruction by maximal voluntary ventilation were impressive indicators of progress. No evidence of hematological, hepatic or renal toxicities was found. Side effects of CS were mild and included brief coughing and wheezing for one to five minutes.

Hannaway PJ, Hyde JS: Scratch and intradermal skin testing: A comparative study in 250 atopic children. *Ann Allerg 28:413-419, 1970*

We have compared results of skin testing by scratch and intradermal methods in 250 atopic children. The following observations are presented:

Intradermal testing is a worthwhile and necessary procedure in infants and young children.

Scratch testing may be an unrewarding procedure under age three, and appropriate intradermals are needed to determine the presence of skin sensitizing antibodies.

Atopic children have variable degrees of skin reactivity, and this reactivity increases with increasing age.

House dust and air-borne molds sensitize during infancy; animal danders and feathers become more important during preschool years; and increased reactivity to pollens is noted by age five years.

Apter JT: Dynamic compliance of living lungs before and after perfusion. *J Biomechanics 3:77, 1970.*

In situ lungs of living, anesthetized dogs were exposed to adequate ventilatory conditions between short exposures to test conditions for measuring some dynamic properties of the lungs. These properties include the dynamic compliance as a function of respiratory cycle frequency and of stroke (or tidal) volume with the lung tissue in various stages of pre- and post-perfusion conditions. Between test exposures, ventilation was maintained with a respiratory rate of 0•4 Hz and stroke volume of 300 ml. Test exposures for computing dynamic compliance as a function of frequency were a tidal volume of 100 ml and rates from 0•04 Hz to 0•9 Hz. At a tidal volume of 100 ml, the lungs behaved linearly, giving a sinusoidal pressure output to a sinusoidal volume input. Test exposures for finding the pressure-volume relationship were performed at a cycle frequency of 0•4 Hz with stroke volumes from 50 ml to 500 ml. Histologically verified pulmonary tissue changes followed steady (non-pulsatile) pulmonary artery perfusion with whole blood for two hours. The viscoelastic properties were a function of the condition of the living tissue.

Because the dynamic compliance was a function only of frequency or of volume or of condition of the lung, there was no hysteresis in these records. They were reversible, reproducible, responsive to verified changes in pulmonary tissue and were consistent with contemporary methods for testing other viscoelastic systems. The tests themselves did not endanger pulmonary tissue properties nor interfere with the gaseous exchange function of the lungs. Therefore, the tests could be adapted for clinical measurements of pulmonary mechanics.

Apter JT, Marquez E, Janas M: Dynamic viscoelastic anisotrophy of canine aorta correlated with aortic wall composition. *J Assn Advan Med Instrum 4:15-21, 1970.*

Longitudinal strips from 14 locations along the aortas of dogs were stretched sinusoidally at frequencies from 0.01 to 10 Hz. *In vivo* longitudinal strain levels were ascertained before these tests and were matched and exceeded during them. The behavior of these strips was compared with the behavior in the circumferential direction and with the behavior of isolated aortic elastin and collagen and of stimulated aortic wall smooth muscle. At strains less than those found *in vivo*, the aorta was generally isotropic, like elastin. At higher strains, matching those found *in vivo*, the upper thoracic aorta behaved like elastin and, again, was isotropic. In contrast, the lower thoracic and abdominal aortas strained to *in vivo* levels behaved like collagen longitudinally and like elastin circumferentially. At still higher strains, where the strain and stress levels were associated with collagen-like properties, anisotrophy was characterized by a higher modulus in the longitudinal than in the circumferential direction. If a slightly strained aorta was stimulated with phenylephrine hydrochloride, the aorta was isotropic and revealed the presence of smooth muscle.

Wilson DM, Apter JT, Schwartz FD: A model for measuring renal blood flow from plasma disappearance of iodopyracet. *J Appl Physiol 28:79, 1970.*

A nonlinear multicompartmented model was developed to be in accord with current understanding of the behavior of iodopyracet (Diodrast) in dogs. Material balance relations applied to each compartment led to equations for the model which was tested in six anesthetized dogs with one kidney removed. The time course of Diodrast plasma concentration changes measured, after a single dose and during infusion, in renal artery and vein as well as in red cells, liver, and muscle established the validity of the model with the assistance of an analog computer solution of the equations. Suitable analysis of these data, using initial slopes and extrema, permitted use of mixed venous blood concentrations, alone, to compute renal plasma flow and renal extraction ratio in four other dogs as well. A large digital

computer programmed to use a nonlinear parameter estimation technique utilized these computations as initial estimates, and all the data as well, to find more accurate values for renal plasma flow and extraction ratio and then to generate computed data for comparison with actual data. Plasma flow and extraction ratio computed this way did differ very little ($P < 0.05$) from clearances measured during constant infusion of para-aminohippurate (PAH). This success suggests that the model may serve as the basis for clinical measurements of these parameters.

BRONCHOESOPHAGOLOGY

Holinger PH, Lederer FL, Soboroff BJ: The TNM classification of cancer of the larynx and pharynx. *Otolarng Clin N Amer 489-495, Oct 1969*

This review article contains a brief description of the Joint Committee classification of cancer. A definition of the anatomical limits of the larynx divides it into supraglottic, glottic and subglottic regions and subdivides each into specific sites. The clinical staging table is based on groups of TN & M combinations having similar prognostic end results. Significant questions have been raised concerning the staging groups, particularly in regard to superficial lesions involving more than one site and whether or not cord mobility has been affected. A discussion of the classification of cancer *in situ* of the larynx suggests that it should be included in Tl.

The anatomical limits of the pharynx include description of the nasopharynx, oropharynx and hypopharynx. By subdividing these regions into sites, more specific designations of tumor location and extent are made. Again, evaluations of staging have been determined by field trials. In contradistinction to the larynx, there is little controversy.

Holinger PH: Klinik und Therapie der Hypopharynx- und Oesophaguserkrankungen. *Published in Germany, HNO 17:129-132, 1969*

This discussion of the endoscopic aspects of diseases of the hypopharynx and esophagus mentions the newer instrumentarium, including flexible lens system fiberoptic illumination esophagoscopes. European and American instruments and technics differ. Physiologic concepts of cricopharyngeal function and the clinical aspects of the esophagogastric junction are related to problems of dysphagia and distal esophageal malfunction. The endoscopic management of pre- and post-operative congenital esophageal strictures, inflammatory lesions including esophagitis, peptic ulcer, hiatal hernia, and cardiospasm are considered. Special emphasis is given to the endoscopic aspects of benign tumors, carcinoma, and the increasingly common problems of post-surgical esophageal strictures. The treatment of Zenker's diverticulum endoscopically, by splitting the cricopharyngeus, has proved to be a satisfactory adjunct to therapy of this condition in selected cases.

Holinger PH: The esophagus. *In Textbook of Pediatrics (9th ed). Edited by W Nelson. Philadelphia, WB Saunders Co, 1970, pp 767-773*

Symptoms suggestive of esophageal disease in infants and children consist of dysphagia, coughing or choking while swallowing, complete inability to swallow, regurgitation of undigested food, hematemesis, and foreign body lodgement. Clinical features of congenital anomalies of various types of esophageal atresia with or without fistula, strictures, vascular compression, and neurologic dysfunction are described. The commonest acquired disease consists of the inflammatory diseases, including those of caustic and corrosive ingestion. A brief description of the foreign-body problem of the esophagus in infants and children is given.

CARDIO-RESPIRATORY

Clark JG, Bucheleres HG, Carleton RA: Endocardial fibrosis detection by cardiac pacing. *Circulation 38:1136, 1968.*

Three patients with endocardial fibrosis who had their endocardial pacing thresholds measured are described. The threshold values were elevated to at least twice normal levels. By determining the endocardial pacing threshold value, a technique is available for detection of endocardial fibrosis during diagnostic cardiac catheterization.

CARDIOVASCULAR SURGERY

Goldin MD, Manax WG, Julian OC: Considerations in planning operative treatment of dissecting aortic aneurysms. *Surg Clin N Amer 50:193, 1970.*

Dissecting aortic aneurysm is a grave condition, especially from the standpoint of pathology, recognition, and management. With the introduction of surgical therapy for this disease, a better understanding of its clinical and pathologic patterns has been obtained. In recent years a great deal of attention has been given to conservative management of dissecting aortic aneurysm, mainly by the use of antihypertensive drugs and bed rest. The results from such medical measures have caused confusion on the part of clinicians in that attempts are made to rigidly classify a given case as either operative or nonoperative. From a statistical point of view, meaningful information insofar as which therapy is most appropriate cannot be obtained by comparison of the two groups. Indeed, the best operative candidate is also the best candidate for medical therapy. Consequently, the medically treated patient who requires surgery becomes a poor candidate for surgical therapy.

The main objective of treatment for this condition is stabilization. But since the various factors attending stabilization cannot be accurately known as plans are made for treatment, it is obvious that we lack a substantial concrete reason for adopting a nonsurgical approach. Moreover, stabilization further shows that even eventually in any study comparing operative and nonoperative therapy, surgical therapy cannot be known to be contraindicated.

ENDOCRINOLOGY

Ryan WG, Schwartz TB, Northrop G: Experiences in the treatment of Paget's disease of bone with mithramycin. *JAMA 213:1153-57, 1970*

The effects of mithramycin, an antibiotic with cytotoxic activity, were observed in 15 patients with active Paget's disease of bone. Mithramycin is shown to have a consistent effect in suppressing the activity of Paget's disease, as reflected by changes in serum alkaline phosphatase and urinary hydroxyproline levels, and the occurrence of symptomatic relief. These responses are probably mediated by a cytotoxic effect on osteoclasts. Several patients have shown prolonged remissions. This agent shows considerable promise as an effective treatment for Paget's disease of bone but means of enhancing the therapeutic :toxicity ratio need further investigation.

Becker FO, Tausk K: Radiologically evident functioning mediastinal parathyroid adenoma. *Chest 58:79-81, 1970*

The presence of a large radiologically evident functioning parathyroid adenoma is in itself rare (five isolated cases reported) but its occurrence in an asymptomatic patient has not

been previously described. Because of the problems encountered in diagnosis and treatment, this case is presented to emphasize the importance of considering the possibility of a parathyroid tumor in the differential diagnosis of mediastinal lesions, even if symptoms are lacking.

Melani F, Ryan WG, Rubenstein AH, Steiner DF: Proinsulin secretion by a pancreatic beta-cell adenoma: Proinsulin and C-peptide secretion. *New Eng J Med 283:713-719, 1970*

In a patient with a pancreatic islet-cell adenoma, fasting serum immunoreactive insulin was 114 to 372 μU per milliliter, about five to 20 times the normal value, but 77 per cent of this "insulin" was found to be proinsulin. After intravenous administration of 1 g of tolbutamide an increase in absolute proinsulin concentration was observed. By means of a specific immunoassay, human C-peptide was detected in the expected elution after gel filtration of serum extracts.

After removal of the adenoma the serum levels of both proinsulin and insulin were very low, and proinsulin represented only 10 per cent of the total immunologic activity. In the tumor tissue, 52 per cent of the total immunologically reactive material was identified as proinsulin.

Taylor SG, Schwartz TB, Zannini JJ, Ryan WG: Streptozotocin therapy for metastatic insulinoma. *Arch Intern Med 126:654-657, 1970*

Streptozotocin, an antibiotic derived from Streptomyces achromogenes, was selected for treatment of a previously diabetic patient with incapacitating hypogylcemia caused by an islet cell carcinoma that had metastasized to the liver. Complete control of all symptoms, together with normalization of biochemical measurements, disappearance of evidence of hepatic metastases as shown on liver scan, and return to his pre-tumor diabetic state, have been accomplished without the development of a serious toxic reaction. This antibiotic appears to be useful in the control of insulinomas not amenable to surgery. Significant laboratory observations over an 80-day period of treatment are presented.

Kornel L, Starnes WR, Hill SR Jr, Hill A: Studies on steroid conjugates: VI. Quantitative paper chromatography of urinary corticosteroids in essential hypertension. *J Clin Endocr 29:1608, 1969.*

To elucidate further our previous findings that patients with essential hypertension produce more sulfate conjugated 17-hydroxycorticosteroids (17-OHCS) and less glucuronide conjugated 17-OHCS than normotensive subjects, individual urinary C_{21} α-ketolic steroids were separated by paper chromatography and quantitated in 11 hypertensives and 11 normotensives. The chromatography was performed separately on free, glucuronide and sulfate conjugated steroid fractions. The results obtained revealed the following statistically significant differences between the two groups of subjects: 1) in the free steroid fraction, excretion of cortisol and cortisone was *higher* in hypertensives; 2) in the glucuronide conjugated fraction, excretion of tetrahydrocortisol, tetrahydrocortisone, tetrahydrocorticosterone and tetrahydro-11-dehydrocorticosterone was *lower* in the hypertensives; 3) in the sulfate fraction, excretion of the most polar steroids, 6α- and 6β-hydroxycortisol, was *higher* in the hypertensives. The ratio of tetrahydrocortisol-to-tetrahydrocortisone glucuronides was also found to be statistically significantly *higher* in the hypertensives. These results: 1) confirm by means of more refined methods our previous findings that production of glucuronide conjugated 17-OHCS in essential hypertension is decreased and production of *polar* sulfate conjugated 17-OHCS is increased, and 2) pinpoint specific steroid metabolites, which are responsible for these changes.

Kornel L, Moore JT Jr, Noyes I: Corticosteroids in human blood: IV. Distribution of cortisol and its metabolites between plasma and erythrocytes in vivo. *J Clin Endocr 30:40, 1970.*

The role of erythrocytes in the metabolism of cortisol *in vivo* was investigated in three subjects who received intravenous injection of tracer cortisol-4-^{14}C. Following administration of the tracer, blood was sampled at 15-to-30-minute intervals for two and one-half hours, and a large blood specimen was obtained at the end of this period. By means of a technique developed by us previously, the following steroid fractions were estimated in the separated and hemolyzed red cells, in a saline wash of red cells, carried out prior to their hemolysis, and in plasma: "free" steroids, "polar free" steroids, glucoronide conjugates, sulfate conjugates and conjugates of a new type, distinctly different from the other two. The results obtained revealed the following: 1) 14 to 20 per cent of the total blood radioactive steroids were "associated" with the red cells; 2) less than half of this amount was "loosely" bound to the cells, presumably adsorbed on the cells' surface and easily removed from the cells by a brief saline wash; concentrations of various free and conjugated steroid fractions in this saline wash were similar to those in plasma; 3) more than half of the steroids "associated" with red cells were more firmly bound to the cells and were not removed from them by the saline wash (they were presumably either bound to the cell membrane or were *in* the cells); the concentrations of various free and conjugated fractions of these steroids were entirely different from those of plasma steroids: 75 to 85 per cent of them were "free" (nonconjugated) compounds, more than one-third of them being more strongly bound to proteins than the ones in plasma; 15 to 25 per cent were in a conjugated form; 4) of the conjugates, only 8 to 14 per cent were glucoronides, whereas 20 to 26 per cent were sulfates; the remaining 62 to 69 per cent were of a new type, so far unidentified, possibly formed within the cells. Individual steroids present in each steroid fraction were identified in the large blood specimens drawn two and one-half hours after the administration of the tracer. It is concluded that there is a differential uptake of various corticosteroid metabolites by red cells *in vivo*, this being due either to different permeability gradients of the cell membrane for various free and conjugated steroids, or due to different affinities of various steroid metabolites for binding by cell membrane or other cell components. This implies that erythrocytes constitute a separate metabolic compartment for cortisol, thus playing an important part in its metabolism.

HEMATOLOGY

Bachmann F: Studies on the effect of pyridinolcarbamate, dextran, heparin, salicylic acid, ϵ-aminocaproic acid and fibrinolytic agents upon changes in the blood coagulation system induced by endotoxinemia. *Excerpta Medica Int'l Cong Series 201, Atherogenesis 1969, pp 87-92, 1969.*

Following the injection of endotoxin in baboons, there was a marked fall in renal artery blood flow and platelet counts. Hypercoagulability and hyperfibrinolysis followed. Late changes were characterized by depletion of the fibrinogen-group factors and of the vitamin-K-dependent factors.

Our studies suggest that the administration of a single drug may not be sufficient to prevent both early and late changes. Drugs inhibiting platelet aggregation either by a direct or indirect mechanism such as pyridinolcarbamate had a beneficial effect upon the early drop of the platelet count and of the renal artery blood flow. More studies are needed, however, to compare the effectiveness of a variety of drugs with each other.

Late changes were favorably influenced by a fibrinolytic agent. Antifibrinolytic therapy worsened the clinical course considerably. It appears, therefore, that maximum benefit may be achieved by a combination of a drug inhibiting platelet aggregation and of a fibrinolytic agent.

NEPHROLOGY

Friedel R, Mattenheimer H: Release of metabolic enzymes from platelets during blood clotting of man, dog, rabbit and rat. *Clin Chim Acta 30:37-46, 1970*

The release of metabolic enzymes from platelets during clotting of blood and the subsequent increase of enzyme activities in serum were studied in man, dog, rabbit and rat. The activities of enzymes were measured which are present in blood cells with high activity (lactate and malate dehydrogenases) and low activity (aspartate aminotransferase). Alanine aminotransferase was included because its activity in blood cells is at the limit of being detectable. Serum was prepared from native plasma and from blood at various times during clotting. The activities of lactate and malate dehydrogenases and of aspartate aminotransferase increased in serum with time during clotting; the increases in man were not large enough to be of significance in routine diagnostic enzymology. The magnitude of the activity increases in serum of the animals was such that enzyme measurements must be made either in plasma or in serum prepared from native plasma. Enzymes are mainly released from platelets and not from other formed elements in the blood. When platelet-rich plasma was allowed to clot, the increase of enzyme activities was similar to the increase observed during the clotting of blood. The pattern of enzyme activity increase in serum resembled closely the activity pattern in platelets.

Pillay VKG, Robbins PC, Schwartz FD, Kark RM: Acute renal failure following intravenous urography in patients with long-standing diabetes mellitus and azotemia. *Radiology 95:633-636, 1970*

In four patients with diabetes mellitus and azotemia, acute renal failure developed after intravenous urography. All had been dehydrated before examination. This, combined with severe vascular disease and proteinuria, appears to cause failure associated with intravenous urography. In all patients with azotemia, and particularly in those with multiple myeloma or diabetes mellitus, adequate hydration before intravenous urography is obligatory. Afterward, fluid intake should be continued, with urine volume being recorded hourly to indicate need for mannitol treatment if the volume decreases progressively.

Pillay VKG, Schwartz FD, Battifora H, Buenger RE, Kark RM: Massive proteinuria associated with vesico-ureteral reflux. *Lancet, Dec. 13, 1969, pp 1272-73.*

Three patients with vesico-ureteral reflux and massive proteinuria are described. The clinical diagnosis in all three was chronic pyelonephritis. Histological examination, however, revealed glomerulonephritis in two and severe nephrosclerosis in one. Massive proteinuria, alone or associated with other renal conditions, is an indication for renal biopsy.

OBSTETRICS

Wolff JR, Nielsen PE, Schiller P: The emotional reaction to a stillbirth. *Amer J Obstet Gynec 108:73-77, 1970*

An interdisciplinary team studied 50 women who lost a baby at or shortly after birth, by means of a series of interviews in the immediate postpartum period. Forty were followed over a three-year span to determine the emotional reaction to the loss and the mechanism of resolution. All reacted with a typical grief reaction. None developed other significant

psychiatric difficulties. In 50 per cent, the resolution was in becoming pregnant again. The remainder used other plans, such as returning to or beginning employment, going to school, or intensifying household and family activities. However, a large number were adamant about not having another baby, and half of these resorted to sterilization. Hospital procedures, patient accommodations, and the attitude of the personnel following the loss played a role in the comfort of the patients but did not seem to affect the eventual outcome.

ONCOLOGY

Northrop G, Taylor SG III, Northrop RL: Biochemical effects of Mithramycin on cultured cells. *Cancer Res 29:1916, 1969.*

The biochemical effects of Mithramycin, an antibiotic employed clinically as an antitumor and antihypercalcemic agent, were studied in mouse embryonic, BHK-21, and Chang's human conjunctiva cell cultures. Following treatment with Mithramycin, RNA synthesis was decreased by 85% in mouse embryo and BHK-21 cell cultures and by 45% in human conjunctiva cell cultures when compared to controls. The inhibition of RNA synthesis in BHK-21 cells was dose-dependent and encompassed all cellular types of RNA. Although Mithramycin inhibited protein and DNA syntheses in BHK-21 cells, these were not dose-related, which suggested that the primary site of action of this antibiotic was on RNA synthesis.

Perlia CP, Gubisch NJ, Wolter J, Edelberg D, Dederick MM, Taylor SG III: Mithramycin treatment of hypercalcemia. *Cancer 25:389, 1970.*

An experience with Mithramycin in the treatment of hypercalcemia of malignancy is reported. Mithramycin given by direct, single, intravenous injection of 25 μg/kg was effective in lowering serum calciums within 24 to 48 hours in the majority of patients studied. The duration of this effect has been quite variable, but repeated doses of single injections have proven to be successful in most cases treated. The potential clinical usefulness of this agent in the treatment of hypercalcemia is apparent. It is reasonable to continue such studies on a long-term basis. Such studies are currently in progress.

PATHOLOGY

Clasen RA, Pandolfi S, Hass GM: Interrupted hypothermia in experimental cerebral edema. *Neurology 20:279, 1969.*

The application of systemic hypothermia to monkeys with cerebral freezing lesions one hour after injury resulted in a diminished weight increment in the damaged hemisphere at twenty-four hours, even though the hypothermia was not sustained. The damaged hemisphere also showed a diminished concentration of water, sodium, chloride, iron, RISA, and dye uptake, when compared with data obtained from untreated animals, but these differences were not statistically significant. It is suggested that the diminished weight increment was a cumulative effect resulting from a decrease in both hemorrhage and edema, and that interrupted hypothermia is an effective means of therapy for this form of cerebral injury.

Coogan PS, Morris F: An improved histologic technic for studying primate retina. *US Air Force Sch Aerospace Med, Sept 1969.*

The histologic technic for preparing primate retina described in this report includes intra-

vascular perfusion with a glutaraldehyde-paraformaldehyde mixture followed by osmium post-fixation and Epon embedding. The technic routinely yields histologic preparations of good quality which are suitable for both light and electron microscopy. The Paragon stain used for light microscopy gave excellent differentiation of receptor cell parts and made it easy to distinguish normal from degenerating receptor cells. The intravascular perfusion of fixative prevented artifactual retinal detachment, thus making this technic useful in studying retinal photic injury.

Eisenstein R, Soble LW, Kuettner KE: Lysozyme in epiphyseal cartilage. *Amer J Path 60:43-54, 1970*

Mouse embryonic femoral cartilage was maintained in organ culture medium to which protamine, toluidine blue or histamine was added. Protamine and toluidine blue induced changes in the staining reactions of cartilage matrix, probably due to an interaction between these anionic substances and negatively charged chondromucoproteins. Protamine also induced an arrest in growth, apparently due to interference with matrix synthesis, which appeared to preferentially affect chondromucoproteins, and a striking hyperactivity of chondrocytes. It is suggested that the protamine effect is due to the inhibition of sulfation of cartilage mucoproteins by protamine, with a reactive hyperactivity in chondrocytes. This system may thus provide a model for the study of cell-matrix interactions in cartilage. By electron microscopy, protamine-chondromucoprotein complexes were easily identifiable, suggesting that small basic proteins may be histochemical markers for these compounds suitable for electron microscopy.

Hass GM, Henson DE, Scott RA, McClain EC, Hemmens A: Influence of cirrhosis on production of atheroarteriosclerosis and thromboarteritis with vitamin D and dietary cholesterol. *Amer J Path 57:405, 1969.*

Groups of rabbits were kept for months on regimens productive of combinations of mild dietary hypercholesteremia, hypervitaminosis D, and carbon tetrachloride-induced hepatocellular disease with progressive cirrhosis. The results led to the following conclusions:

1. Chronic hepatocellular damage and subsequent cirrhosis due to carbon tetrachloride did not produce sufficient change in levels of serum cholesterol to influence development of atheroarteriosclerosis. Modifications which occurred were attributed to inhibition of intercellular matrix formation by proliferating arterial intimal mesenchyme and to increased sensitivity to the vasculotoxic action of vitamin D.
2. Mildly hypercholesteremic animals without hepatocellular disease were unharmed by a periodic dosage of 50,000 IU of vitamin D, while the same periodic administration of 100,000 IU promptly produced lethal generalized calcific atheroarteriosclerosis. Animals with hepatocellular disease and cirrhosis proved to be exceptionally sensitive to vitamin D so that dosages as low as 12,500 IU quickly caused lethal calcific atheroarteriosclerosis, complicated at times by thromboarteritis restricted to small vessels supplying muscle. The incidence of thromboarteritis and the severity of calcific arterial disease were directly proportional to the severity of hepatocellular disease, the amount of vitamin D given periodically, and, to a lesser extent, the degree of moderate hypercholesteremia.
3. Periodic administration of 100,000 IU of vitamin D always produced medial calcific degeneration of several peripheral arterial systems. This degeneration in animals with normal hepatic function stimulated fibrocellular proliferation of the adjacent intima and, in the presence of sufficient hyperlipemic hypercholesteremia, there was an accumulation of lipids in the proliferating intimal mesenchyme. In animals with reduced hepatic function due to administration of carbon tetrachloride, there was no decrease in calcific medial arterial degeneration or serum cholesterol levels but fibrocellular intimal proliferation was inhibited. Hence, there was a conspicuous reduction in newly formed intimal matrices which favor intimal lipid accumulation. This seemed to be the principal factor preventing development of severe intimal atheroarteriosclerosis in animals with hepatocellular disease.

4. Two experimental conditions which greatly enhance the vasculotoxic action of vitamin D have not been defined. One is chronic hepatocellular damage as described in this report. The other, described in a previous report, is chronic administration of nicotine. The two conditions produce about the same result. This indicates that there may be a common pathogenesis involving hepatic mediation of vitamin D action as it relates to the regulation of calcium ions in release and activation of the biogenic amines.

PEDIATRICS

Christian JR, Pisani AL, Shannon I: Community child care: The role of the neighborhood health center. *Illinois Med J 136:67 1969.*

The decade ahead will reveal how well we have managed the many crises which face this state and this nation: the poverty crisis, race crisis, hard core unemployment crisis, and the health crisis—all the related crises that make up the so called "Urban Crisis." This presentation is concerned with the health crisis, more specifically the crisis in child care.

Our medical schools and teaching hospitals must develop new ways of bringing their resources to bear on the urgent health problems of our cities. These institutions have to get away from their woefully inadequate traditional approaches and remedies to the health crisis with which we are faced, a crisis so serious that it is termed by many a "national disaster."

It is mandatory that new approaches to the delivery of health care be created. The development of the neighborhood health center represents one such new approach to comprehensive family-oriented medical care for poverty areas.

Pisani AL: Child health care in the inner city: The neighborhood health center approach. *Bull Pediat Pract 3:1, 1969.*

The aim of the Mile Square Health Center is to improve the health care of a poverty population by making available comprehensive family-oriented health services within a designated neighborhood. The center is concerned with all aspects of health care including environmental, psychological and socioeconomic. The availability of preventive, diagnostic, consultative and therapeutic services including home follow-up of minor and chronic illness has enabled the Center to render 98.4 per cent of all pediatric care on an ambulatory basis, a fact which might interest pediatric educators whose training programs continue to be in-patient oriented.

PSYCHOLOGY

Garron DC: Theoretical note: Sex-linked, recessive inheritance of spatial and numerical abilities, and Turner's syndrome. *Psychol Rev 77:147, 1970.*

Sex-linked, recessive transmission of superior spatial and numerical abilities has been inferred from male superiority and from greater unlike-sex than like-sex parent-child similarity. Impairments of these abilities in women with Turner's syndrome is also viewed as implicating the sex chromosome complement in the expression of these abilities. It may be shown, however, that women with Turner's syndrome should be superior in these abilities if transmission is sex-linked and recessive. Although the specific hypothesis is not supported, there is evidence suggesting that the sex chromosome complement and related sex differences in biochemical processes may underly sex differences in these abilities.

Leavitt, F: Accuracy of report and central readiness. *J Exp Psychol 81:542, 1969.*

Weiss (1965) has suggested that warning signals affect response by inducing change in central rather than peripheral or motor processes. The present set of experiments tested the prediction that the slope of the performance curve following warning is similar for different performance measures. Preparatory intervals of 200, 500, 1,500, and 4,000 msec. were employed to assess the effects of warning on two response measures, accuracy of report and reaction time. The results showed the pattern of response at different points following warning to be the same for the two measures of performance. Since the results remain the same, though the response is changed from finger movement to the spoken word and the measure from speed to accuracy, support for central process involvement was inferred.

SURGERY

Pemberton LB, Witkowski LJ: The indications for total gastrectomy. *Surg Clin N Amer 50:57, 1970.*

The four indications for total gastrectomy are gastric neoplasms, the Zollinger-Ellison syndrome, necrosis of the stomach, and stress ulcers. Certain entities, such as necrosis of the stomach or a malignant tumor of the proximal 70 per cent of the stomach, are straightforward, accepted reasons to perform total gastrectomy. Although the treatment for Zollinger-Ellison syndrome is total gastrectomy, the diagnosis can be difficult to establish, and the pancreatic tumors are not discovered in 25 per cent of the patients at the time of surgery. The choice of operation for patients suspected of having this syndrome often requires the surgeon to make a difficult operative decision. Finally, stress ulcers are poorly understood and unpredictable and usually involve emergency operations. The surgical treatment of multiple superficial ulcers of the stomach requires the most mature surgical judgment to decide whether to perform a total gastrectomy.

UROLOGY

Merricks JW, Papierniak FB: Traumatic rupture of the testicle. *J Urol 103:77, 1970.*

Four cases of traumatic rupture of the testis are described. None of the patients were seen by a urologist immediately after injury. The surgical salvage rate was 50 per cent.

Immediate exploration is advised for scrotal trauma to prevent loss of testicular function. Many of the recently recorded testicular ruptures occurred during sports participation. Some type of improved scrotal protector might aid in preventing such injuries.

VIROLOGY

Dienhardt F, Wolfe LG, Theilen GH, Snyder, SP: ST-feline fibrosarcoma virus: Induction of tumors in marmoset monkeys. *Science 167:881, 1970.*

Two newborn marmosets, inoculated with a cell-free extract of feline fibrosarcomas, developed multiple sarcomas and died within 46 days of inoculation, whereas two of these animals inoculated with a crude homogenate developed no tumors. This susceptibility to a mammalian RNA sarcoma virus suggests that marmosets may be particularly suitable for attempts to isolate infectious agents from man.

Deinhardt F: Hepatitis in subhuman primates and the hazards to man. *In: Infections and immunosuppression in subhuman primates. Munksgaard, Copenhagen, Balner & Beveridge, 1970*

1. Several subhuman primate species either harbor their own hepatitis viruses or can become infected with human hepatitis viruses. The nature of these agents and their relationship to human hepatitis viruses will only become clear once reliable assay systems to determine the antigenic identity of these viruses have been developed.

2. Subhuman primates overtly or covertly infected with hepatitis viruses can infect man and, therefore, caution should be exercised, particularly in handling recently caught, juvenile subhuman primates. Human gamma-globulin prophylaxis has been used in individuals at high risk and this practice appears justified.

3. Hepatitis can be induced in marmosets by inoculation of materials from human hepatitis cases and, in contrast to other primates, the disease can be passed serially from marmoset to marmoset. The agents causing the experimental hepatitis in marmosets are probably human IH viruses, but irrespective of the identification of the agents as human or marmoset viruses, the disease in marmosets is a reliable primate model for the study of hepatitis. An understanding of its pathogenesis and detailed characterization of the responsible agents could only help in the continuing search for methods of demonstrating human and possibly other primate hepatitis viruses by cell culture and immunological methods.

4. Australia antigen and antibody occur in a number of subhuman primate species but the significance of these findings is unclear at this time.

Deinhardt F: Nutritional requirements of marmosets. *In Feeding and Nutrition of Nonhuman Primates. New York, Academic Press Inc, 1970, pp 175-182*

Adequate diets, chosen by trial and error rather than by rationale, have been fed juvenile white-lipped tamarins and cottontop marmosets. It seems there are no "marmoset-specific" nutritional requirements for those species which have been maintained in laboratories, but to my knowledge controlled study of such needs has not been done. The diets in use have been shown to be adequate by the survival and breeding of the animals but variations and omissions from these described diets would almost certainly provide equally good results as long as minimum requirements, as yet undetermined, were met.

Deinhardt F: Current trends in use of marmosets in virological research. *Ann NY Acad Sci 162:551, 1969.*

The characteristics of certain species of marmoset monkeys as laboratory primates are reviewed and their use as experimental animals in several virological studies is outlined briefly. Studies of oncogenic viruses, part of a search for the agents of human malignancies such as leukemia and lymphomas, revealed that some sub-species of *Saguinus fuscicollis* were regularly susceptible to the Schmidt-Ruppin strain of Rous sarcoma virus. Similarly, some sub-species of marmosets were susceptible to human viral hepatitis, a disease for which no other experimental animal exists.

Holmes AW, Ogden JD, Deinhardt F: Marmosets in microbiological research. *Alnima Models for Biomedical Research II, Publ 1736, National Academy of Sciences, Washington, D.C. 1969.*

Some results of seven years of experience maintaining and handling marmosets in a microbiology laboratory are described. These animals have been relatively easy to manage. Experimental studies have shown that it is possible to induce malignancies in them with Rous sarcoma virus and to produce a disease very much like human viral hepatitis by the inoculation of infectious human serum.

Marczynska B, Treu-Sarnat G, Deinhardt F: Characteristics of long-term marmoset cell cultures spontaneously altered or transformed by Rous sarcoma virus. *J Nat Cancer Inst 44:545, 1970.*

Cells from a kidney obtained by unilateral nephrectomy of an adult male marmoset (*Saguinus fuscicollis*) were established in cell culture and exposed to Schmidt-Ruppin Rous sarcoma virus (SR-RSV) at various passage levels. In five independent experimental series, only one culture of six inoculated cell lines was transformed by SR-RSV when the cells were inoculated in the G_1 phase. The transformed cells formed foci of sarcoma cells in culture vessels, retained a normal diploid chromosome complement, grew in soft agar, and produced a tumor after transplantation into the original kidney-donor animal. The same cells, however, did not grow as microtumors after implantation into hamster cheek pouches. No infectious virus could be recovered from the cells transformed *in vitro* even after co-cultivation with chick embryo fibroblasts, but infectious SR-RSV was recovered by the same technique after the cells had grown as a sarcoma in the autologous animal. Of seven uninoculated cell lines and five lines inoculated with SR-RSV but not transformed, five permanent cell strains were established. All five cell strains have been maintained *in vitro* for about four years. The emergence of permanent cell strains was or was not accompanied by morphological and/or chromosomal alterations. The chromosomal changes consisted of a reduced number of diploid cells with concomitant appearance of bizarre chromosomes such as dicentrics, rings, or extra large chromosomes. None of the spontaneously altered or unaltered cells grew in soft agar nor did they induce tumors on transplantation into the original kidney donor or into hamster cheek pouches. These observations are important in the current consideration of the use of cell culture lines or strains for the production of viral vaccines.

Maynard JE, Shramek G, Noble GR, Deinhardt F, Clark P: Use of attenuated live mumps virus vaccine during a "virgin soil" epidemic of mumps on St. Paul Island, Alaska. *Amer J Epidem 92:301-306, 1970*

During a "virgin soil" epidemic of mumps at St. Paul, Alaska, live attenuated mumps virus vaccine was administered to a portion of the population to determine its efficacy as a current anti-epidemic measure. Also, a number of adults had received two doses of inactivated mumps virus vaccine two years prior to the epidemic, enabling determination of the residual efficacy of this material. The majority of individuals receiving killed vaccine failed to show detectable serum neutralizing antibody against mumps two years subsequent to immunization, and no decreased risk of illness or infection could be demonstrated for this group. A marked reduction in clinical illness rate in relation to the non-vaccinated comparison group was shown only for those individuals receiving live vaccine who were over the age of 24. However, administration of live virus vaccine was likely responsible for extinction of the epidemic prior to exhaustion of the pool of susceptibles.

Tischendorf P, Wolfe LG: Extramedullary hematopoiesis in marmosets following blood loss. *Lab Anim Care 20:697-702, 1970*

Extramedullary hematopoiesis (EMH) developed rapidly in the livers of marmosets bled over 40 per cent of their blood volume weekly but disappeared one to two weeks after the hematologic values returned to normal. Hematologic changes and EMH were not observed in healthy marmosets bled 8.5 to 9.5 per cent of their blood volume weekly for eight weeks. Extramedullary hematopoiesis was found in the liver, spleen, adrenal glands, kidneys, and lung of fetuses and of tumor-bearing marmosets that died following severe chronic blood loss. Hepatic hematopoiesis was observed in livers of marmosets up to 15 days of age. The histology and location of EMH within the different organs were described.

Tischendorf P, Shramek GJ, Balagtas RC, Deinhardt F, Knospe WH, Noble GR, Maynard JE: Development and persistence of immunity to Epstein-Barr virus in man. *J Infect Dis 122:401-409, 1970*

The distribution of antibodies to Epstein-Barr virus (EBV) in an isolated Alaskan population and in a mixed population from the Chicago area was studied. All individuals over two years of age in the Alaskan population had antibodies to EBV; in the Chicago population 86 to 100 per cent of individuals four years of age or older had EBV antibodies. Geometric mean titers remained constant and elevated in both populations regardless of age. Primary EBV infections in early childhood expressed themselves as minor febrile illnesses usually with pharyngitis, tonsillitis, and mild lymphadenopathy without the development of heterophile antibodies. The association of EBV with typical infectious mononucleosis during adolescence and early adulthood has been further confirmed, and suggestive evidence has been obtained for restimulation of EBV antibodies during other febrile illnesses. A study of four cases of American Burkitt's lymphoma failed to show an association with EBV.

Junge U. Hoekstra J, Wolfe L, Deinhardt F: Microtechnique for quantitative evaluation of *in vitro* lymphocyte transformation. *Clin Exp Immun 7:431-437, 1970*

A microtechnique is described to quantitate *in vitro* transformation of lymphocytes from man and marmosets following stimulation by PHA and different antigens. The C-thymidine uptake of lymphocytes grown in cultures of 0·06 to 0·2 ml of whole blood was measured by liquid scintillation. The magnitude, consistency and reproducibility of the results were similar to those achieved using cultures of purified lymphocytes or cell-rich plasma but fewer technical procedures were required.

Laufs R, Walker W.: Metabolic and virologic studies in primate liver organ cultures. *Proc Soc Exp Biol Med 133:1006, 1970.*

Adult primate liver explants were maintained in culture for up to three weeks. The liver explants maintained their histological identity, the cellular metabolism remained active, and the explants supported the multiplication of a number of DNA and RNA viruses during the period of *in vitro* cultivation.

Butler JW, Butler MK, Marczynski B: Automatic analysis of 835 marmoset spreads. *Ann NY Acad Sci 157:424, 1969.*

The main objective of the present work is the study of cytogenetic effects caused by oncogenic viruses. In the preliminary work, it was necessary to test the performance of Chloe digital computer systems for cytogenetic analysis on large populations of normal cells. The existing system of computer programs has been under development at Argonne National Laboratory for the past five years. The mean and variance of the chromosome number, the estimated total chromosome area, and the area spectrum of the chromosome complement were studied. Data on system rejection rates and accuracy of karyotype estimation have also been accumulated. The results indicated the need of some improvement of both METAPHAZ and SUMMARIZ programs and the necessity of employment of more sophisticated statistical methods.

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HEPATITIS-ASSOCIATED ANTIGEN: CURRENT STATUS

A. William Holmes

INTRODUCTION

The careful epidemiological observations of Dr. Lürman of Bremen, during an outbreak of jaundice in 1883 and 1884, suggested to him that his patients had become infected during vaccination against smallpox with a preparation of human lymph.[1] Since that time many other outbreaks of needle-transmitted hepatitis have been described. The largest was the epidemic of 50,000 cases which occurred in personnel of the United States Armed Forces who received yellow fever vaccine during World War II. Clinical experience and human volunteer experiments[3] in the late 1940's and early 1950's clearly established a distinct form of hepatitis transmitted by the inoculation of human serum, with an incubation period substantially in excess of that commonly accepted for infectious hepatitis. Nonparenteral transmission of serum hepatitis had been suggested as long ago as 1938[4] but that report was discounted until it was established, in at least one group of extensive human volunteer studies, that long-incubation-period hepatitis can be transmitted not only by transfer of serum or plasma parenterally, but also by the ingestion of infectious serum or plasma.[5] The serendipitous observation by Blumberg and his co-workers of a new antigen in the serum of an Australian aborigine, and the subsequent association of this antigen with long-incubation-period hepatitis, form the basis for this review. Although new data about this antigen, originally called "Australia Antigen" but now properly referred to as hepatitis-associated antigen (HAA), become available every month, enough has been learned already to indicate that it is of considerable importance to the clinician, the epidemiologist, and to those interested in the banking and transfusion of human blood or blood products.

THE DISCOVERY OF HAA

While studying serum lipoproteins as genetic markers in primitive and civilized populations, and with the use of serum from patients having had multiple transfusions as a source of antibody, Blumberg and his co-workers found a new antigen in the serum of an Australian aborigine.[6] A survey of a general hospital population showed that this antigen was particularly likely to be found in the serums of patients with Down's syndrome, hepatitis, and a variety of leukemias.[7]

The association with hepatitis was subsequently confirmed by Prince[8] and by Gocke.[9] Prince suggested that HAA is

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specifically associated with serum, or long-incubation-period hepatitis. With improved sensitivity of methods and studies of larger populations this association has become more clear while the association of HAA with other diseases *not* primarily involving the liver seems to be not so definite.

ASSOCIATION WITH SPECIFIC KINDS OF HEPATITIS

Serum Hepatitis

While early reports of the study of random samples of serum showed that patients with the clinical diagnosis of serum hepatitis had a greater likelihood (an average of 62 per cent of patients in a total of eight studies) of having demonstrable HAA in their serum than patients with the clinical diagnosis of infectious hepatitis (an average of 16 per cent of patients in a total of six studies) it has become clear that where multiple samples are available, particularly from the early phase of the disease, the association of HAA with serum hepatitis (long-incubation-period hepatitis, homologous serum jaundice, hepatitis B, SH) approaches 100 per cent. Giles and her coworkers infected 34 volunteers with plasma containing their "MS-2" agent. This plasma was positive for HAA and the hepatitis induced by it carries an incubation period varying from 41 to 108 days. Thirty-three of the 34 volunteers so infected demonstrated HAA in their serum during the course of their hepatitis; it appeared early, usually about forty days after inoculation, and was present usually only in the early phase of the clinical disease which occurred anywhere from a few days to a few weeks later.[10] Serums were also available from 130 volunteers infected with an icterogenic plasma pool in studies of serum hepatitis carried out by Murray between 1951 and 1954.[4] Ninety-three per cent of these volunteers had HAA demonstrable in their serum in conjunction with their hepatitis. In sixty of these it could be shown that the serum became positive for HAA about three to four weeks before the development of hepatitis; in about half of these patients the antigen had disappeared by the fourth week of the disease. In occasional patients only a single specimen was positive. It seems clear then that HAA is closely associated with classic serum hepatitis. When specimens are collected early in the course of the disease and where multiple specimens can be examined, this association approaches 100 per cent.

It is of particular interest that in Murray's group of patients, in the group studied by Giles et al., and in some patients observed by Redeker and his coworkers,[12] HAA persisted in the serum long into convalescence. Their patients were usually those who had a mild disease in the acute phase but whose disease merged into a more chronic, persisting hepatitis, without striking symptoms—often only with elevated serum transaminase values, but with persisting low-grade hepatitis in their liver biopsies. Barker and Murray have suggested that a mild case of HAA-positive hepatitis may carry a greater risk of developing into chronic persisting or unresolved viral hepatitis than the overt clinical form of the disease.[13]

Infectious Hepatitis

Where epidemiologic evidence points to a common source outbreak of orally transmitted, short-incubation-period hepatitis, serums of patients from such epidemics have been found to be consistently negative for HAA. In a typical epidemic caused by contamination of the water supply with sewage, more than 600 cases of hepatitis occurred in an isolated mining community in northern Ontario. One hundred-two samples were collected from patients within the first week of clinical disease, and in only one individual was HAA detected.[14] There is no good summary of all other outbreaks which have been studied but at least fifteen similar outbreaks, occurring around the world, have been studied by various groups and shown *not* to be asso-

ciated with a significant incidence of HAA in the serums of the patients with infectious hepatitis.

Endemic Hepatitis

In most patients who come into the general hospital with viral hepatitis the cause is not apparent. If the patient has been exposed to human blood by transfusion or the sharing of needles, his disease is usually labeled serum hepatitis. If he gives no such history, and especially if he has had some nonparenteral contact with other individuals with jaundice, he is usually thought to have infectious hepatitis. As mentioned earlier, a small percentage of patients who appear on clinical grounds to have infectious hepatitis have HAA in their serum. This has forced a reconsideration of our thoughts about the nonparenteral transmission of this disease. Krugman and his co-workers had indicated some years ago that the form of long-incubation hepatitis which they labeled "MS-2" could be transmitted by the feeding of infectious serum to volunteers. Acute-phase stool of patients with MS-2 hepatitis did not transmit the disease to volunteers. We need not presume, therefore, that the small percentage of patients who do *not* give a history of parenteral exposure, yet who have HAA-positive hepatitis, are concealing certain aspects of their histories from us. At least one small outbreak has been described in which HAA-positive hepatitis is extremely likely to have been transferred by the serum-oral route to ten contacts.[15]

Chronic Persisting Hepatitis

We may define chronic persisting hepatitis as a disease which often begins with an attack of typical acute hepatitis, which persists for a period in excess of twelve weeks, which is associated with biochemical evidence of persisting hepatocellular injury but is not associated with persisting abnormal immune phenomena such as smooth muscle antibody, antinuclear antibody, positive lupus cell preparations or striking increase in serum gamma globulin or IgG. It can be anticipated that about 30 per cent of such patients will have HAA detectable in their serum. A number of reports have given figures at variance with this, but it seems clear that the variation is due to inconsistency in the definition of the disease by respective authors. In some European studies this percentage has approached 70 per cent, but again insufficient details are given to evaluate the meaning of the figures.

Chronic Active Hepatitis

Chronic active hepatitis differs from chronic persisting hepatitis in that it often has an insidious onset with distinct evidence of hepatocellular injury which is often not severe, which may be associated with cirrhosis and with antinuclear or smooth muscle antibodies or positive LE-cell preparations, and with impressive elevations of serum gamma globulin and IgG concentration. Using this definition, three groups have reported that the incidence of HAA in chronic active hepatitis approaches zero.[16-18] This has been our own experience as well.

Drug-Induced and Alcoholic Hepatitis

There appears to be no association between HAA and alcoholic hepatitis or either hepatocellular or cholestatic drug reactions.[19]

ASSOCIATION WITH OTHER LIVER DISEASES

Cirrhosis

There is no association of HAA with either post-necrotic or alcoholic cirrhosis.[19] A single report found that nine of ten patients with primary biliary cirrhosis had HAA present in their serums[20] but our own study of ten such patients and the study of a much larger group (70 patients) by Klatskin have failed to confirm this observation.

Hepatoma

Studies are just beginning to appear of the incidence of HAA in patients with hepatoma. It is clear that there is a fairly

high incidence in such patients in Uganda whereas this relationship is not nearly so clear in temperate areas. It has been suggested that viral hepatitis can be related to the genesis of some of these hepatomas, but much more study will be needed before any distinct relationship can be confirmed.

THE INCIDENCE OF HAA IN NORMAL HUMANS

In their earliest reports on the incidence of HAA in various populations Blumberg and his co-workers pointed out that while only one in 1000 normal Americans carried HAA, this carrier rate was much higher in a variety of tropical populations, varying from two to as high as 20 per cent. Most of these tropical populations have not been studied in terms of the incidence of chronic liver disease, but it is hard to believe that, for instance, 20 per cent of the Cashinahua Indians of the Upper Amazon have either acute or chronic persisting hepatitis. A small group of natives of the Island of Cebu have been studied over a period of years and while some of the HAA-positive natives had slightly higher serum glutamic pyruvic transaminase (SGPT) values than their matched HAA-negative controls, it was clear that none of the individuals in either group had impressive evidence of liver disease.[21] The significance of this high carrier state in these tropical populations in terms of liver disease awaits careful biochemical and morphological studies of the livers of such individuals. The high incidence in the tropics, however, when compared with the virtual absence of the antigen in the equally primitive Eskimos, has reawakened interest in the possibility of the transmission of HAA and therefore, perhaps, hepatitis from biting insects.

Considerable variation in the incidence of HAA exists in apparently normal populations in the United States. A group of 8,000 blood donors in the Rochester, Minnesota area had an incidence of HAA-positivity of 0.057 per cent.[22] Another group of 1,300 donors who were inmates of Philadelphia prisons had an incidence of 3.14 per cent.[23] Other, apparently normal, donor populations have varied between these two extremes. It has been suggested by both Klatskin and Peters that all individuals with circulating HAA have abnormal livers. The experience of these investigators has shown that even if biochemical tests are normal, the livers are not normal on biopsy. Their experience may be biased by the fact that they both have studied large groups of patients with overt liver disease and have made these observations during the follow-up of such patients. Krassnitzky and his co-workers studied sixty HAA-positive donors and found that 37 per cent had abnormal hepatic tests.[24] No biopsies were done. Thirty-two HAA-positive donors have been discovered in our own blood bank and eight of these had some abnormality of hepatic tests. In most cases this was confined to a minor elevation (less than 100 units) of SGOT or SGPT activity. One donor had overt jaundice as well. We have not had the opportunity to perform any biopsies either. The meaning of a positive HAA test in an apparently normal individual is, therefore, not yet clear. Until we understand this phenomenon better, such patients should probably undergo careful study, including liver biopsy, to exclude the presence of chronic liver disease.

THE INCIDENCE OF HAA IN DISEASES WHICH ARE NOT PRIMARILY HEPATIC

Down's Syndrome

In one of the earliest papers discussing HAA, Blumberg and his co-workers reported that this antigen occurred in 29.8 per cent of a group of 84 institutionalized patients with Down's syndrome.[7] In extending these studies further they found that the high incidence of HAA-positivity in Down's syndrome was restricted to

patients who were institutionalized and was not found in patients cared for at home.[25] Subsequent studies by other authors have confirmed these observations.[26,27] The suggestion has been made that the possibilities for nonparenteral transmission of HAA-positive hepatitis are good in a large institution for mentally retarded children and that this might explain this high incidence. It also has been found, however, that matched control retardates living in the same institutions but without Down's syndrome have a much lower incidence of HAA in their serums.[25,26] While Blumberg's group has suggested that these patients have a peculiar form of chronic hepatitis, the evidence is not sufficiently good to verify this. It has been suggested that the Down's syndrome patients have a genetic predisposition to contract hepatitis and develop persisting HAA antigenemia, but the issue has by no means been settled at this time.

Leprosy

Patients with lepromatous leprosy who live in areas where HAA is relatively common in the normal population (the Philippines, India) have been found to have antigenemia with an incidence of about twice that of the normal surrounding population.[28] In regions where the antigen is rare in healthy people (coastal Brazil) HAA is equally rare in the patients who have lepromatous leprosy.[29] There is no such relationship of HAA with tuberculoid leprosy. A disordered, immune mechanism has been postulated to explain the high level of antigenemia in lepromatous leprosy, but again the issue remains open.

Leukemias

Sutnick, et al., have reported that in 688 patients with various kinds of leukemia the frequency of serum HAA positivity is seven per cent.[30] This is, of course, substantially higher than the incidence in the general population in this country. Early reports suggested that this related in some way to the genesis of leukemia, but careful study of the patient populations has indicated that this high incidence correlates quite well with a prior history of transfusion. It has been pointed out that the incidence is higher in this group of transfused patients than in a group not suffering from leukemia, and it has again been suggested that defective immunity in some leukemics allows antigenemia to persist in a situation when it otherwise would not.[30]

Polyarteritis Nodosa

Many years ago a report described four patients with polyarteritis nodosa whose disease had presented initially as hepatitis presumed to be related to yellow fever vaccination which had occurred within the preceding 60 to 120 days.[31] Little more was made, however, of any association between polyarteritis and hepatitis until the report of Gocke, et al., of four more cases of polyarteritis in which an illness resembling hepatitis had been present at the onset and in whom HAA was present in the serum.[32] Subsequently, three other cases have been mentioned in two other reports associating these two diseases.[33,34] The observation of Gocke, et al., that HAA could be identified immunologically by fluorescent antibody technique in the diseased vessel wall has aroused interest in the possibility that an abnormal immune reaction to HAA, or some inherent predisposition in rare individuals, could trigger the onset of polyarteritis in at least some cases. Larger groups of patients need to be studied before we will have any definitive answers to these questions.

General Considerations: Immunity and Heredity

The above diseases have in common some alteration of immune responsiveness. Evidence has also been presented that the tendency to develop HAA in the serum could be inherited as a simple autosomal recessive trait.[35] Shulman has offered cogent arguments to counter this, and it is his conclusion that the presence and persistence of HAA in the serum of

patients in any of these populations is more likely to correlate with age at the time of exposure, size of the infecting dose, and frequency or duration of exposure.[36] This argument could apply to the patient with Down's syndrome and lepromatous leprosy. It would not explain completely the apparently higher incidence of the carrier state in leukemics or the cases of polyarteritis. With regard to the theory of inheritance, it should be remembered that while genes run in families, so also do infections and it will be difficult to separate these two influences.

IS HAA A VIRUS?

Soon after the first reports of the association between HAA and hepatitis, reports began to appear indicating that materials containing HAA had in them small 20μ particles and that these particles could be aggregated by antiserum to HAA.[37] These particles could be separated from serum by ultracentrifugation and were found to have a buoyant density of 1.21 in cesium chloride, which is consistent with the density of some known viruses. These particles could be made heavier (density changed to 1.27) by treatment with ether, suggesting that there was an important lipid component in the particles.[38] Dane and co-workers have more recently reported larger particles, about 42μ, bearing some similarity to the smaller particles previously described. They have suggested that these larger particles represent complete virus whereas the smaller particles represent incomplete virus.[39] While these particles share some characteristics of size, appearance, and density with known viruses, complement-fixation tests have shown no antigenic relationship to 300 different serotypes of viruses sharing some of these characteristics with HAA.[40] The essential parts of a virus, are, by definition, a nucleic acid core and some kind of protein coat.[41] Viruses characteristically contain either DNA or RNA but not both. It is important, therefore, to note that in spite of extensive and sophisticated studies of purified preparations of HAA, only one unconfirmed report has suggested the presence of any nucleic acid at all.[42] This one report suggests that there is some RNA in the HAA particle; if true, this would overcome one of the largest stumbling blocks to classifying HAA as a virus.

When HAA-containing serum or plasma is inoculated into humans, there is a latent period of about 40 to 50 days during which HAA cannot be detected in the serum of the recipient. It then appears in the serum in considerable quantity, and persists in most cases until the early phase of clinical hepatitis which may occur from days to weeks later. It then characteristically disappears from the serum relatively early in the course of the hepatitis.[43] This evidence of propagation in the human host, with HAA in the serum at the time at which one would expect a viremia to occur, has been cited as evidence that this is in fact a virus particle. The close association with a specific disease, namely serum hepatitis implies that this is in fact serum hepatitis virus. In spite of this, except for extremely sensitive radioimmunoassay techniques, it has not been possible to find HAA antibody in the convalescent phase of HAA-positive hepatitis.

The issue then remains open. If the stumbling blocks of apparent absence of nucleic acid and apparent absence of antibody response to acute infection could be overcome, and particularly if HAA could be propagated in a tissue culture system (which also has not yet been demonstrated), then even the skeptics would be forced to concede that HAA very likely is serum hepatitis virus.

METHODS OF ASSAY FOR HAA

It is not intended that this review should dwell in detail on the technical aspects of the various methods for the detection of HAA. It should be noted that the earliest technique used for the detection of this antigen, the Ouchterlony immunodiffusion assay, was a rela-

tively insensitive technique. As laboratories have worked with this antigen, techniques for identification by complement fixation, and immuno-osmo-electrophoresis have been devised. There is also now available a somewhat tedious but extremely sensitive technique utilizing radioimmunoassay. Shulman has discussed these techniques and their relative sensitivity in detail.[36] There is no question that the relatively low incidence of HAA in patients with hepatitis in early reports was related to insensitivity of the technique and to the obtaining of blood samples randomly in the course of the disease. The important point is, however, that there is now available a technique (specifically, immuno-osmo-electrophoresis) which is sensitive, specific, and rapid (one hour). Commercial kits are coming on the market which supply reagents and materials which will make it possible for even the smallest hospital or clinic to assay serums with a high degree of accuracy at low cost.

WHAT IS THE USEFULNESS OF HAA ASSAY?

Diagnosis

The association of HAA with long-incubation-period or serum hepatitis has been already discussed. It is clear that the physician who has a patient with the classical clinical features of viral hepatitis does not need HAA assay to tell him from what his patient is suffering. There are always problem-patients, however, in whom the evidence of hepatocellular injury is not as clear as it might be and in whom some features of the disease are distinctly atypical. In these patients it should be a diagnostic help to be able to demonstrate HAA in the serum. It should be remembered that one will rarely encounter a carrier of this antigen and that this carrier state is likely to be more common in those who have used illicit parenteral drugs or who have been given transfusions of blood or blood products in the past and that there are, therefore, some situations where this test may be misleading. It is safe to say, however, that the patient with acute hepatocellular disease and a positive serum-HAA assay should be presumed to have hepatitis until proven otherwise. Further, the desirability of careful study of the apparently normal individual with a positive serum HAA test has already been mentioned.

Prognosis

Persistence of HAA in the serum into the convalescent phase of hepatitis has clearly been associated with persistence of liver injury and transition into chronic persisting hepatitis.[12] There is, therefore, some prognostic value in repeating the HAA test in patients whose serum is positive in the acute phase of the disease at intervals of about every two weeks.

The Prevention of Post-transfusion Hepatitis

It was suggested in some of the earlier studies of HAA that bank blood containing this antigen could account for a portion of the cases of post-transfusion hepatitis which are observed. Two reports have suggested that the incidence of hepatitis in patients receiving HAA-positive blood may be as high as 50 to 75 per cent.[9,44] It is clear from these reports, however, that patients receiving HAA-negative blood also get hepatitis although at a substantially lower rate. A consideration of a few figures which are available, and some of these are anecdotal, would suggest that the exclusion of HAA-positive blood from the bank would result in the exclusion of about two per cent of the blood drawn and reduce the incidence of post-transfusion hepatitis by about two-thirds. This would be a gratifying reduction at a low cost, but it would leave us with a significant number of patients still getting hepatitis as a result of our prescribed therapy. It does not absolve us of our responsibility as physicians to use every means at our disposal to promote voluntary and replacement donation of blood.

It is only in this way that the amount of blood which must necessarily be bought from commercial sources can be reduced and it is only through this means that we can hope to reduce the residual number of cases which will still occur.

SUMMARY

The discovery and characterization of the hepatitis-associated antigen have contributed greatly to our understanding of the two forms of viral hepatitis. It is clearly associated with long-incubation-period or serum hepatitis and appears to have no relationship to short-incubation-period or infectious hepatitis. Its role in the pathogenesis of other diseases which are not primarily hepatic is not yet clear. Although it shares many characteristics with viruses, and its association with serum hepatitis is in many ways like the association of other viruses with the diseases which they cause, the absolute demonstration that the particle called hepatitis-associated antigen is *the virus* of serum hepatitis is still to come. Detection of HAA in serum can be of help in diagnosis and prognosis and is likely to be of considerable help in excluding units of blood likely to transmit hepatitis. However, not *all* infected units of blood will be detected in this way.

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EFFECT OF ORALLY ADMINISTERED SODIUM BICARBONATE ON SIGNS AND SYMPTOMS IN MULTIPLE SCLEROSIS: PRELIMINARY COMMUNICATION

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INTRODUCTION

We recently reported[1,2] that scotomas, nystagmus, and oculomotor paresis in patients with multiple sclerosis (MS) are transiently improved by the intraveneous administration of sodium bicarbonate, disodium edetate (Na_2EDTA) and also by hyperventilation, procedures that have in common the ability to lower the concentration of serum ionized calcium. This improvement is believed to be due to an increase in axonal excitability which results in a restoration of conduction in some demyelinated central nervous system (CNS) fibers. The following working hypothesis was proposed.

The ratio of the action current generated by a nerve impulse to the minimum current density needed to maintain conduction is known as the conduction safety factor.[3] This ratio reflects the net effect of many variables such as action potential magnitude and duration, membrane threshold, axoplasmic resistance, etc. which are involved in the maintenance of axonal conduction. If the safety factor is decreased by injury or disease to a value less than one, conduction cannot occur. If a drug or chemical can increase the ratio to one or more, conduction will be restored. It is postulated that in MS some nerve fibers are in a nonconducting but labile state with safety factors slightly less than one and that conduction can be restored by appropriate chemical means. Since lowering the concentration of calcium ions bathing an axon causes a decrease in threshold[4] it would be expected to increase the safety factor, i.e. the minimum current density needed to maintain conduction is decreased. This working hypothesis has received strong support from earlier studies in aminals[5,7] and MS patients.[1,2]

In the present study we have sought to determine whether the beneficial effects seen previously with intravenous sodium bicarbonate can also be produced with large amounts of orally administered sodium bicarbonate. In addition to visual

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changes, effects on gait abnormalities, which were not tested in the earlier studies, have also been observed.

METHODS

Eight patients were studied, seven female and one male. Table 1 summarizes pertinent clinical data. Patient selection was based on the presence of readily demonstrable visual and/or gait abnormalities. All patients had a firm diagnosis of multiple sclerosis and fulfilled the important criteria of remitting course and disseminated lesions.

Gait performance over a short, fixed course was recorded by cinematography. In some experiments tandem walking (heel-to-toe) was also filmed. The ability to perform rapid foot tapping was tested with a simple electromechanical device: a signal proportional to foot position was recorded on a Sanborn DC strip-chart recorder. The frequency of tapping rather than the amplitude was examined. Hand-tapping was monitored with a telegraph key that closed a circuit applying a voltage to the recorder; here, too, frequency was the variable examined.

Visual acuity was measured in two ways. An *Armed Forces Near Visual Acuity Test* chart was used at intervals throughout the experiment. Measurements of far vision (nine feet) were obtained by displaying two identical vertical lines on an oscilloscope screen. The distance separating the two lines was slowly and continuously increased until the subject responded that two lines could be seen; five to seven trials with each eye (tested monocularly) were obtained and averaged. Knowing the distance from the screen to the subject and the distance separating the two lines at threshold it is possible to calculate a visual acuity in terms of the minimum visual angle for perception. Since the intensity of the vertical lines and the level of room lighting did not conform to standard ophthalmological conditions these values cannot readily be expressed in terms of standard clinical acuity values.

In some experiments visual fields were plotted by means of a tangent screen and

TABLE 1

PATIENT SUMMARY

Patient	Sex	Age	Duration of Disease	Exacerbations and Remissions	Evidence for Dissem. Lesions	Most Recent Exacerbation
D.C.	F	30	5.3 yrs.	Yes	Visual scotomas Paraparesis	4 years (Slowly progressive since)
E. D.	M	43	11 yrs.	Yes	Visual scotoma Paraparesis	9 years (Slowly progressive since)
M. F.	F	27	2.3 yrs.	Yes	Nystagmus Visual scotoma	3 months prior to first experiment (in exacerbation at last experiment)
D. P.	F	38	2.6 yrs.	Yes	Paresthesias Bilat. visual scotomas	10 months
K. S.	F	26	1.6 yrs.	Yes	Visual scotoma Paraplegia	At time of testing
E. W.	F	38	10 yrs.	Yes	Visual scotoma Paraplegia	14 months
P. W.	F	32	3 yrs.	Yes	Visual scotoma Ataxia	2 years
L. W.	F	29	3.8 yrs.	Yes	Visual scotoma (Paresis rt. leg and arm)	10 months

standard hand-held targets.

Experiments were carried out in the following manner. After obtaining control responses and a control venous blood sample the patient was started on sodium bicarbonate orally in the form of 600 mg capsules. The chemical was administered approximately every thirty minutes until a total of 39 to 48 grams had been given. The dosage schedule for each experiment is given in Table 2. Testing and blood sampling were carried out at intervals during and following the period of drug administration. Testing was usually continued until the responses had returned to a base-line state.

In some experiments an Instrument Laboratory, Inc. pH/Gas Analyzer was used to obtain values for pH, pCO_2, and pO_2 on venous blood; calculation yielded a value for total base excess. In other experiments venous samples were only analyzed for total CO_2 combining power using standard techniques.

RESULTS

The oral administration of sodium bicarbonate produced varying degrees of improvement in each patient tested; in three (M.F., D.P. and L.W.) the effects on visual acuity and/or gait were marked. The results are summarized in Table 3.

Subject L.W., on first testing (1-29-71), showed a moderate improvement in gait but she reported that upon returning home in the evening there was a further dramatic improvement in gait, and in addition her vision markedly improved. This effect began while in transit (approximately one and one-half hours after leaving the laboratory) and lasted for approximately two to three hours.

Subsequent testing of this patient (2-3-71) confirmed this response. Her baseline gait which was characterized by an almost continuous "buckling" at the right knee and an absent associated right arm swing gradually improved and be-

TABLE 2

DOSAGE SCHEDULE (In Grams) FOR EACH EXPERIMENT

SUBJECT	EXPERIMENT												TOTAL DOSE
D. C.	2-10-71	6	6	6	3	3	3	3	3		6	6	45
E.D.	2-5-71	12	6	3	3	3	3	3	3	3			39
M. F.	12-18-70	12	3	3	3	3	3	3	3	3	3	6	3	48
	1-18-71	12	6	3	3	3	3	3	6					39
	2-24-71	6	6	6	3	3	3	3	3	3	3	3		42
D.P.	3-12-71	6	6	6	6	3	3	3						33
K. S.	3-17-71	6	6	6	6	3	3	3	3	3				39
E. W.	3-19-71	6	6	6	6	3	3	3	3	3				39
L. W.	1-29-71	12	6	3	3	3	3	3	3	3				39
	2-3-71	12	6	3	3	3	3	3	3	3	3	3		45
	2-19-71	12	6	3	3	3	3	3	3	3	3	3		45
P.W.	2-12-71	6	6	6	6	6	6	6						42
		0	30	60	90	120	150	180	210	240	270	300	330	
		TIME (Min)												

TABLE 3

SUMMARY OF RESULTS WITH ALL SUBJECTS*

Subject	Experiment	Total Dose (Grams)	Visual Acuity	Visual Fields	Gait	Rapid Alternating Movements	
						Foot	Hand
D. C.	2-10-71	45	0		+	0	
E. D.	2-5-71	39			+	0	
M. F.	12-18-70	48	+++	+++	++	+++	
	1-18-71	39	++		++	++	
	2-24-71[a]	42	+		0		
D. P.	3-12-71	33	+++[b]	+++[b]			
K. S.	3-17-71	39	0		0	+	0
E. W.	3-19-71	39			0	++	+
L. W.	1-29-71	39	0[c]		++[c]		
	2-3-71	45	+++		+++		
	2-19-71	45	+++		++		
P. W.	2-12-71	42	0		0	++	

* Space is blank when abnormality not present or not monitored

0 No change

\+ Slight improvement

++ Moderate improvement; patient may be aware of change

+++ Marked improvement; patient also aware of change

a Subject in acute exacerbation

b Improvement lasted 3 days and subject returned to baseline on 4th day; fields retested 3-19-71

c Subject reported dramatic improvement at home that began approximately 1.5 hours after end of experiment

came normal except for a slight decrease in her arm swing. Paralleling this improvement there was a gradual increase in visual acuity. Vision in the left eye improved strikingly, with acuity going gradually from a visual angle of 5.52 min of arc in the morning (control level) to an acuity of 3.48 min of arc by 7:55 p.m., an improvement of 37 per cent. Table 4 shows the progressive changes in acuity. It is noteworthy that both findings (gait and vision) returned to control levels before the termination of the experiment.

Subject M.F. demonstrated equally dramatic changes with oral sodium bicarbonate. During her first experiment (12-18-70) visual fields were plotted throughout the day, and a marked improvement occurred in a central scotoma present in her right eye; its size decreased and it gradually disappeared in the macular region leaving only a small paracentral defect. This change was accompanied by an improvement in near visual acuity. These results are presented in Figure 1.

In the second experiment with M.F. (1-18-71) improvements again occurred with oral sodium bicarbonate. Visual acuity (peak improvement 22 per cent), gait, and the ability to perform rapid foot tapping (peak improvement of 68.3 per cent) were all improved. Table 5 contains the results from the visual acuity and the foot-tapping tests.

TABLE 4

SUBJECT: L.W. EXPERIMENT: 2-3-71

Time	Oral $NaHCO_3$	Visual Acuity Min. of Arc (% Change*)
9.22 (Control)		5.52
	Started ↓	
11:40	Stopped	5.14 (6.9)
1:40		5.50 (0.4)
2:45		5.35 (3.1)
5:00		5.39 (2.3)
6:00		4.24 (23.2)
7:55		3.48 (37.0)
9:10		3.54 (35.8)
10:06		5.25 (4.9)

*Per cent difference between control value and value at any time during experiment.

As noted in Table 3, at the time of M.F.'s third experiment (2-24-71) she was in a stage of acute exacerbation. Although her visual acuity improved slightly with oral bicarbonate, her gait remained unchanged.

D.P. had bilateral central scotomas with markedly decreased visual acuities which had remained constant over the preceeding 10 months. During the course of the experiment there was a gradual decrease in the size of the scotoma in the right eye. Visual acuity improved markedly (patient aware of change) along with this change in visual fields. Surprisingly, these changes reversed only slightly during the period of the experiment. After three days of improved vision she reported a return to her pre-experimental state on the fourth day. Three days later her fields and acuity were tested in the laboratory and were found to be similar to the previous control state. Representative visual fields can be seen in Figure 2.

Changes in blood chemistry produced by the orally administered sodium bicarbonate were not systematically monitored in these studies. Although in some experiments pH and pCO_2 were determined, in others only values for total CO_2 combining power were obtained. While the available data supports the idea that the observed improvement is related to a metabolic alkalosis it is not now possible to correlate the degree of alkalosis with the degree of neurological improvement.

DISCUSSION

This study demonstrates that clinically significant improvement in signs and symptoms of multiple sclerosis can occur with large amounts of orally administered

TABLE 5

SUBJECT: M.F. EXPERIMENT: 1-18-71

TIME	Rate of Foot-Tapping—taps/sec (% change*)		Visual Acuity—Min. of Arc (% change*)	
	R	L	R	L
10:30 Control	2.2	3.4	3.4	4.1
1:45	3.3 (50.0)	3.6 (5.9)	3.2 (5.9)	3.3 (19.5)
2:35	3.7 (68.3)	4.2 (23.5)	2.8 (17.6)	3.2 (22.0)
3:35	3.5 (59.0)	4.1 (20.6)	3.4 (0.0)	3.4 (20.6)
4:10	2.9 (31.8)	3.6 (5.9)	3.3 (2.9)	3.4 (20.6)
4:45	2.7 (22.7)	3.2 (—5.9)**	3.9 (—14.7)**	4.5 (—9.8)**

* Per cent difference between control value and experimental value. Positive values indicate an improvement, negative values a worsening.

**These values indicate an overshooting which is frequently seen and is transient. Its significance is not known.

sodium bicarbonate. This phenomenon is probably identical to the transient improvement of visual and oculomotor signs seen with the intravenous administration of sodium bicarbonate (discussed in detail in previous studies from this laboratory[1, 2]).

These effects are believed to be due to an improvement or restoration of impulse conduction in some demyelinated CNS axons. As mentioned briefly in the Introduction, this is postulated to be the consequence of an increase in the conduction safety factor brought about by the

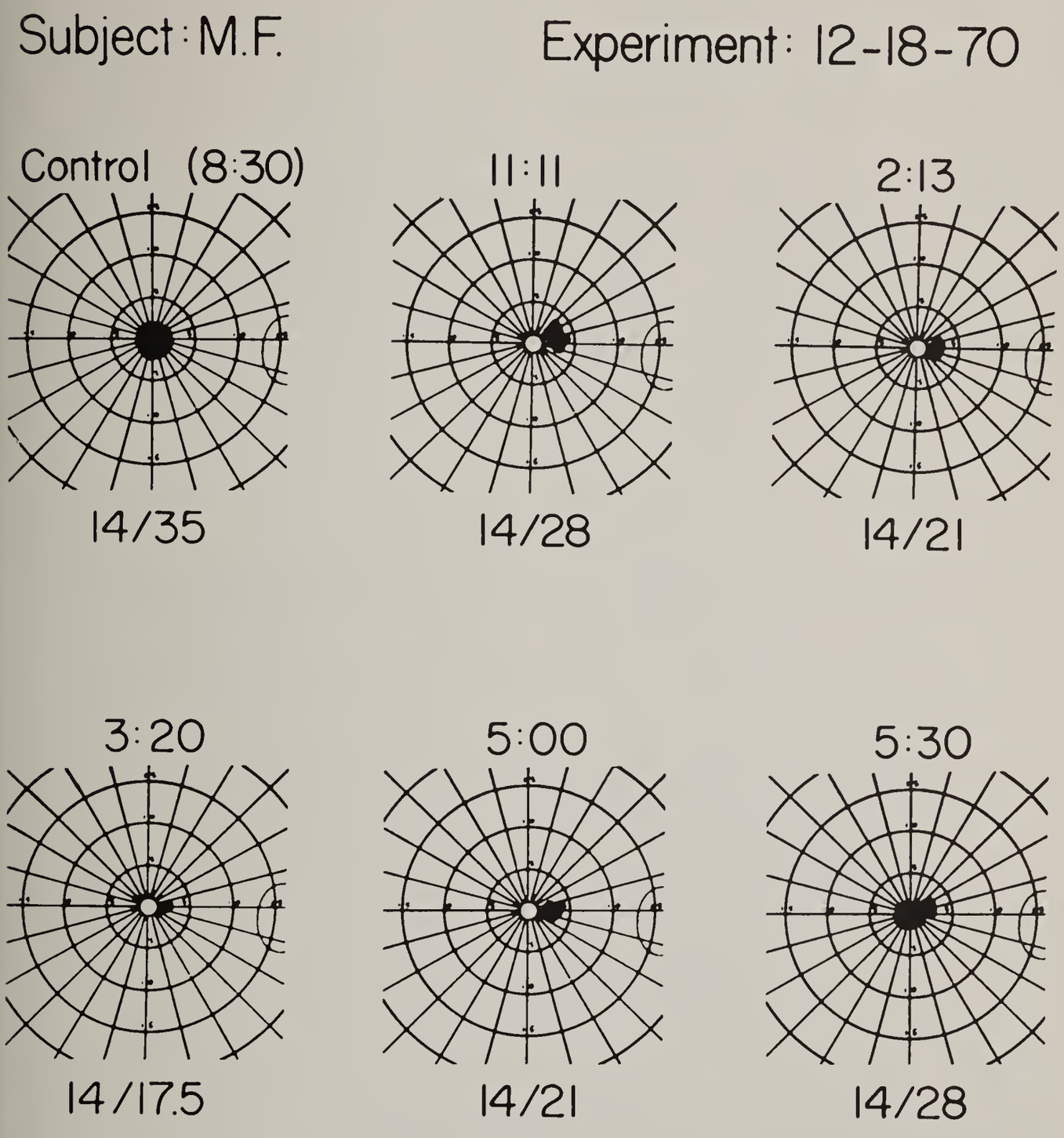

Fig. 1—Visual fields and near visual acuities for patient M.F. (12-18-70). Acuity is given below each field map. A total of 48 grams of sodium bicarbonate had been taken by 2:00 p.m. Note that the decrease in scotoma size and the return to control levels occurs gradually. Improvement in gait and the ability to perform rapid foot tapping accompanied this dramatic improvement in visual function.

threshold-lowering effect of decreased serum ionized calcium which in turn results from the metabolic alkalosis induced by sodium bicarbonate.

As in our previous studies[1, 2] two aspects of the experimental protocol are of partic-

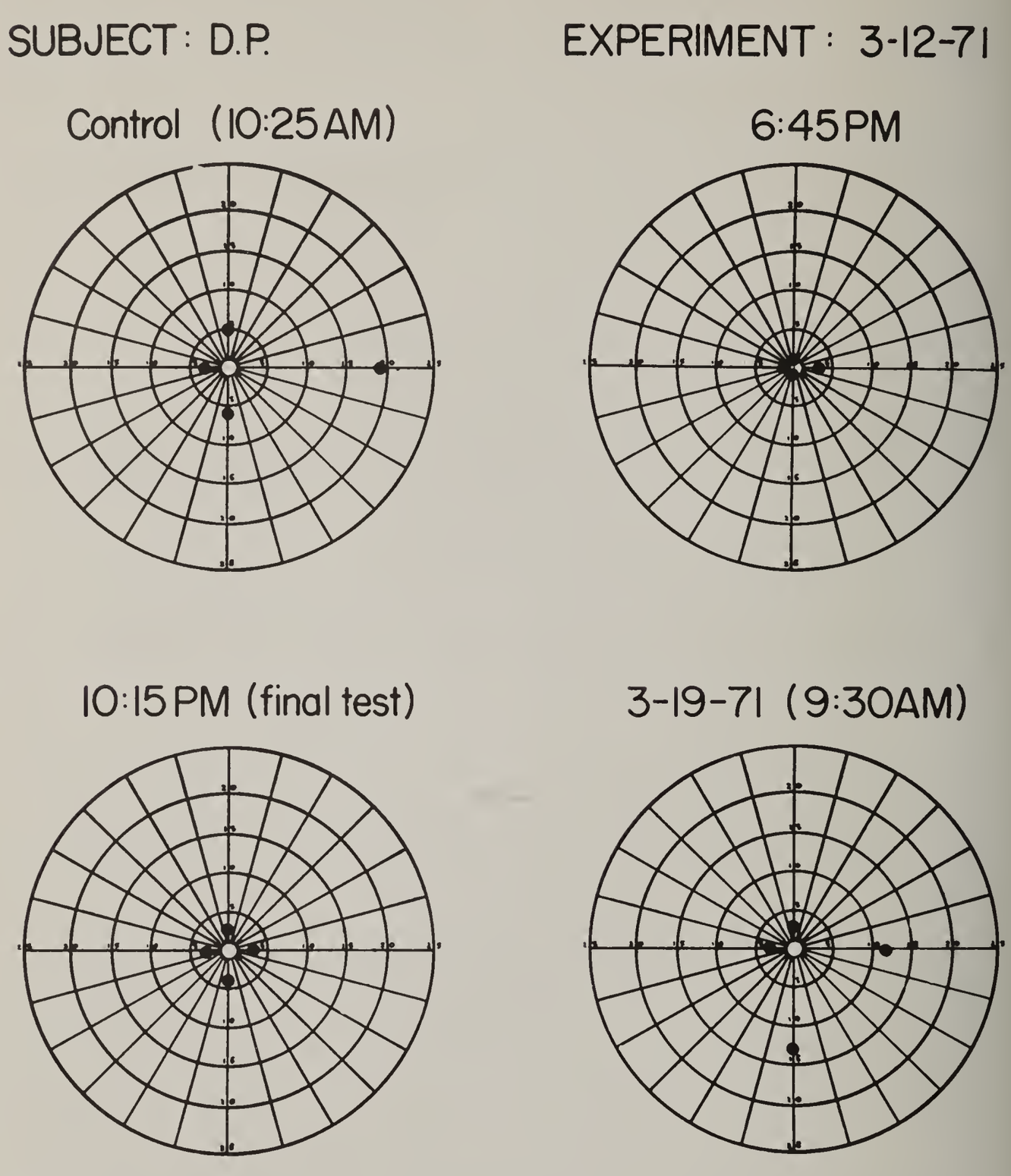

Fig. 2—Visual fields for patient D.P. A total of 33 grams of sodium bicarbonate had been taken by 1:25 p.m. Only four points in the field were determined (along the horizontal and vertical meridians) in order to shorten the duration of each test. For this reason the scotoma outline cannot be drawn, and only the four monitored points are shown. By the end of the experiment (10:15 p.m.) the decrease in size of the scotoma had only minimally reversed. Full reversal probably didn't occur until the fourth day after the experiment (by the patient's report). One week after the initial experiment the scotoma more closely resembled the previous control state. (Bottom, right field.)

ular importance. The first is that the experiments are relatively acute, lasting at most 12 to 14 hours, and that the improvement produced by the drug reverses during the period of testing. (The one significant exception to this, D.P., experienced a prolonged improvement, although with an eventual reversal; there is no adequate explanation for this at present.) Thus the observed effects are unlikely to be related to the characteristic remitting course of the disease and are most reasonably attributed to the alterations in the internal environment produced by the administered chemical. Second, an attempt has been made to utilize quantitative methods of testing neurological function in order to obtain data as objectively as possible. Vision has been monitored in this way, but gait has so far proven difficult to quantitate. However, the availability of films of a patient's gait make a reasonably accurate semi-quantitative assessment possible.

The practical clinical significance of improving signs and symptoms of MS patients with oral administration of sodium bicarbonate must be accompanied by a note of caution. First, it has proven difficult to produce reliably a marked metabolic alkalosis with orally administered sodium bicarbonate. Each patient has reacted in an individual manner, with the rate of change of pH and the final level reached varying considerably. Furthermore, the two subjects tested more than once demonstrated differences in their response to the drug from experiment to experiment. This is probably related to variations in the rate of drug absorption and effectiveness of pulmonary and renal compensatory mechanisms which tend to counteract the alkalosis. A second reason for caution is the fact that not every subject responded to the induced alkalosis with the same degree of improvement. This, of course, is not unexpected, since the working hypothesis assumes a population of nonconducting axons with the potential for being restored to function. Variations in the size and functional importance of this population would govern the extent of improvement possible. Thus, a patient's response to sodium bicarbonate may fluctuate markedly as the underlying pathology changes during clinical remissions and exacerbations. For these two reasons it must be stressed that not all MS patients can be expected to respond as favorably as did M.F., D.P. and L.W. in this study. It is clear that sodium bicarbonate is not a practical agent for clinical use in multiple sclerosis.

Nevertheless, the clinical significance of this report lies in the demonstration that signs and symptoms of MS can be improved by specific chemical alterations in the internal environment induced by orally administered drugs. Though these clinical effects are symptomatic in nature and can have no effect on the progression of the disease there is little doubt that they can substantially add to a patient's functional ability. The goal here is to improve that part of the diseased CNS which is still viable and capable of functioning. Future studies will be directed toward the search for a clinically feasible means of increasing the conduction safety factor in multiple sclerosis.

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ESTROGENS IN DISSEMINATED BREAST CANCER: COMPARATIVE STUDY OF PHYSIOLOGIC VERSUS PHARMACOLOGIC DOSE

Esteban Guevara
Charles P. Perlia
Janet Wolter

INTRODUCTION

Since the first report to the Council on Pharmacy and Chemistry in 1947[1] on the usefulness of sex steroid hormones in postmenopausal women with disseminated mammary cancer, androgens and estrogens have been used without significantly varying the dose originally recommended. Subsequent reports[2-6] have pointed out the side effects of these substances and confirmed the results obtained initially.

There have been no reports of any studies comparing physiologic doses of estrogens with the standard antitumor dose, which is many times the physiologic dose. If the side effects could be eliminated by reducing the dose of the hormone without changing the antitumor effect, more patients with breast cancer might be benefited by estrogen administration.

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METHODS

Patient selection and classification was done according to the master protocol of the Cooperative Breast Cancer Group.[7] All patients had a histological diagnosis of breast cancer and evidence of clinically progressing metastases. Patients with no previous additive hormone therapy for breast cancer were selected for random study. They were grouped as to dominant site and number of years after menopause.

The baseline work-up consisted of history and physical examination, hemogram and urinalysis, x-ray film of the chest, x-ray bone survey, liver function tests, and serum calcium determinations. All measurable lesions were tabulated and photographed if visible. The patients received tablets containing either 0.2 mg or 5.0 mg of diethylstilbestrol to be taken three times daily. Identification of the coded dose was kept in a sealed envelope. If patients failed to show a response, or progressed within two months, the dose level was identified. Those patients who had been receiving the low dose were given the high dose.

Duration

The drug had to be given for at least eight weeks before treatment was considered evaluable. When the disease remained static, or regressed, the hormone was continued until evidence of progression.

EVALUATION

Three kinds of response were determined by physical examination and measurements in soft tissue and liver disease, and by x-ray films in bone and lung lesions:

1. Progression: Previously measured lesions increased in size, or new lesions appeared during the two-month period;
2. Static: The lesions remained unchanged and no new ones appeared;
3. Regression: Measured lesions disappeared or decreased in size by 50 per cent or more, and the osteolytic bone lesions showed evidence of recalcification.

Subjective feelings of well-being and pain relief were not considered signs of regression.

MATERIAL

Sixty-four patients were entered in the study, most of them from the University of Illinois Tumor Clinic. Their ages ranged between 40 and 85 years; 35 patients were white, and 29 black; the right breast was involved in 32, the left in 28, and both breasts in four; 58 patients were postmenopausal and six premenopausal at the time of initial diagnosis of the primary disease. Of the menstruants, three underwent oophorectomy, one received radiation to her ovaries, and two experienced a natural menopause before the development of metastases.

The initial treatment was radical mastectomy in 44 patients; 21 of these received postoperative radiation and six received some kind of adjuvant chemotherapy. The interval clinically free of disease following primary therapy varied from six months to 15 years. The remaining 20 patients were considered to have primary inoperable lesions: five underwent palliative simple mastectomy (followed by radiation in three and chemotherapy in one); two patients received radiation therapy only; and 13 received no therapy prior to the study (Table I).

Of the 64 patients, 33 received 0.6 mg of stilbestrol per day, and 31 received 15.0 mg (Table II).

Side effects were severe enough to prevent 14 patients from continuing the hormone. Six of these were in the low-dose group and eight in the high-dose. Toxicity consisted of nausea and vomiting in six women, hypercalcemia in four, fluid retention causing congestive heart failure in one, vaginal bleeding in one, skin rash in one, and evidence of hepatocellular damage in one.

Seven patients were lost to follow-up.

RESULTS
(See Table III)

Definite progression was seen in four to 12 weeks in 27 patients: 18 in the low-

TABLE I: INITIAL TREATMENT

Adjuvant Therapy	Main Initial Therapy			
	Operable	Inoperable		
	Radical Mastectomy	Simple Mastectomy	Radiation Therapy	None
Radiation therapy	21	3	0	0
Chemotherapy	6	1	0	0
None	17	1	2	13
TOTAL	44	5	2	13

dose group and nine in the high-dose.

The disease remained static from five to 12 months in eight patients; three in the low-dose group and five in the high-dose.

No regression was seen in patients in the low-dose group.

A sustained regression for 1½, 6, 6, 7, 12, 16, 18, and 22 months was seen in eight patients in the high-dose group. This affected soft tissue lesions in five, pulmonary nodules in one, pulmonary and skin lesions in one, and pleural effusion in one.

Of the patients on the low dose who showed progression, 10 received a second course with the high dose. Further progression was seen in nine, and no change in one (Tables IV and V).

TABLE II: RESULTS

	Unable to Evaluate		Evaluable	Total
	Due to toxicity	Lost to follow-up		
Low dose	6	6	21	33
High dose	8	1	22	31

TABLE III: RESPONSE

	Low Dose	High Dose	High Dose after Low Dose
Progression	18	9	9
Static	3	5	1
Regression	0	8	0
Total	21	22	10

TABLE IV
DISTRIBUTION ACCORDING TO POSTMENOPAUSAL YEARS

Years Postmenopause:	0 to 5	5 to 10	10 or over	Total
Dose: 0.6 mg.				
Progression	3	3	12	18
Static	0	0	3	3
Regression	0	0	0	0
	3	3	15	21
Dose: 15.0 mg.				
Progression	1	2	6	9
Static	0	2	3	5
Regression	0	2	6	8
	1	6	15	22

TABLE V
DISTRIBUTION ACCORDING TO DOMINANT SITE

Dominant Lesion:	Soft Tissue	Osseous	Visceral	Total
Dose: 0.6 mg.				
Progression	9	5	4	18
Static	1	0	2	3
Regression	0	0	0	0
	10	5	6	21
Dose: 15.0 mg.				
Progression	4	1	4	9
Static	4	1	0	5
Regression	5	0	3	8
	13	2	7	22

COMMENT

The age, race, initial treatment, and duration of free interval did not seem to influence the response to estrogen therapy. Side effects were not intolerable except in the 14 cases in which the drug had to be discontinued. These were seen at both dose levels.

Ten patients whose disease progressed on the 0.6 mg dose received a second trial with 15.0 mg. No regression was obtained with this higher amount. It is possible that the low dose in some way interfered with the beneficial effect of the higher dose, inasmuch as several regressions would be expected in a 10-patient sample. However, the number of observations is too small to justify a definite conclusion.

SUMMARY

Physiologic and pharmacologic doses of stilbestrol were given to 64 patients with disseminated breast cancer in a double-blind study; no regression was obtained with the former; the response obtained with the latter was comparable to that reported previously (25 to 30 per cent). Side effects are not significantly different between the two doses.

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HEALTH MANPOWER NEEDS: THE ENTRY-LEVEL ALLIED HEALTH STUDENT: A CASE STUDY

Peter J. Farago, M.D.
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Elizabeth Siegel

INTRODUCTION

Almost a year ago we reported on a joint venture between the Chicago Community Colleges and Rush-Presbyterian-St. Luke's Medical Center to train individuals for positions in the allied health field.[1] The principal aim of that report was to describe the pilot program. The original project was initiated in the Fall of 1967, with the premise that training individuals at the entry level *would* help meet the immediate need for allied health workers and, at the same time, prepare more people for advanced training.

The original program was aimed at recruiting a largely untapped manpower resource: the adult poor outside the current labor market; certain people who though employed were in dead-end jobs within the health field; and recent high school graduates and other young people motivated toward medical careers but lacking the skills and background to train directly for professional status. We felt that all these persons could begin their education at intermediate nonprofessional levels and continue to professional status if the proper "career ladders" were built into the structure of the program. For example, an individual trained to become an inhalation therapy aide might progress to registered inhalation therapist with an Associate of Arts degree in a period of two to three years.

The "short-term program" was 28 weeks in length with the first 14 weeks concentrating on the didactic aspect of training ("core curriculum") and the second 14 weeks centering on clinical experience with supportive classroom instruction. After completion of the "core curriculum" a student could elect clinical training in one of eleven job areas. We believed that this kind of "core course-clinical experience model" would allow the students to gain a broader orientation to the health-occupation field and enable instructors to operate from a standardized base of instruction which could be integrated into a specific category of occupational duties and responsibilities. (For a more detailed account of courses offered in the core curriculum and areas of clinical training see Reference 1.)

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The purpose of this paper is twofold: First, to report on the preliminary results with respect to evaluation of some of the initial participants and, second, to view the entire program in light of its effect on the allied health field. A few comments need to be made at the outset. Since the major concern of the implementors was program initiation, baseline data gathering was not emphasized. Nevertheless, certain useful information on students' background was collected prior to their participation in the program and is summarized. All participating students received the didactic portion of their training at Malcolm X Community College which was known as Crane City College at the time the program started. Data on students' progress after completion of the program pertain to some of those individuals in the first six classes who received their clinical training at Presbyterian-St. Luke's Hospital. During the first two years of the short-term program about 70 per cent of the participants received their clinical training at this medical center.

EARLY PARTICIPANTS IN THE PROGRAM

Background

Of the 285 early participants in the program, 94 per cent were female, and 191, or two-thirds, were over 25 years of age. Almost all were Black. This group of participants had an average of slightly more than three children each, ranging from no children to ten, with the majority having two children. Over three-fourths lived in community areas classified as poverty zones, with the majority coming from the Near West and South side areas of Chicago.

Only 42% of the 285 had graduated from high school, and of these only seven had any formal education beyond that level. Thirty-five of the participants had an eighth-grade education, and the remaining 132 had some high school but did not graduate.

Measurements of reading and mathematics levels were obtained for 258 and 238 of these student participants respectively. The following tables summarize the results.

TABLE I

Reading Levels of 258 Participants in the Short-term Program

Number	Level
10	5th Grade
101	6th Grade
89	7th Grade
39	8th Grade
14	9th Grade
5	10th Grade

TABLE II

Mathematics Levels of 238 Participants in the Short-term Program

Number	Level
61	5th Grade
143	6th Grade
28	7th Grade
6	8th Grade

Many students accepted for enrollment received additional financial support. Most of these were allotted special funds under Aid to Dependent Children (ADC). Many others were eligible for aid from Manpower Development Training Act (MDTA).

Training Experience—The Clinical Areas

Data available on 258 enrollees in the first three classes showed an over-all dropout rate of 50 per cent. Of the dropouts, 80 per cent terminated their training during the first three months, or clinical training period. Exact records were not kept, but counselors from the community college reported that many

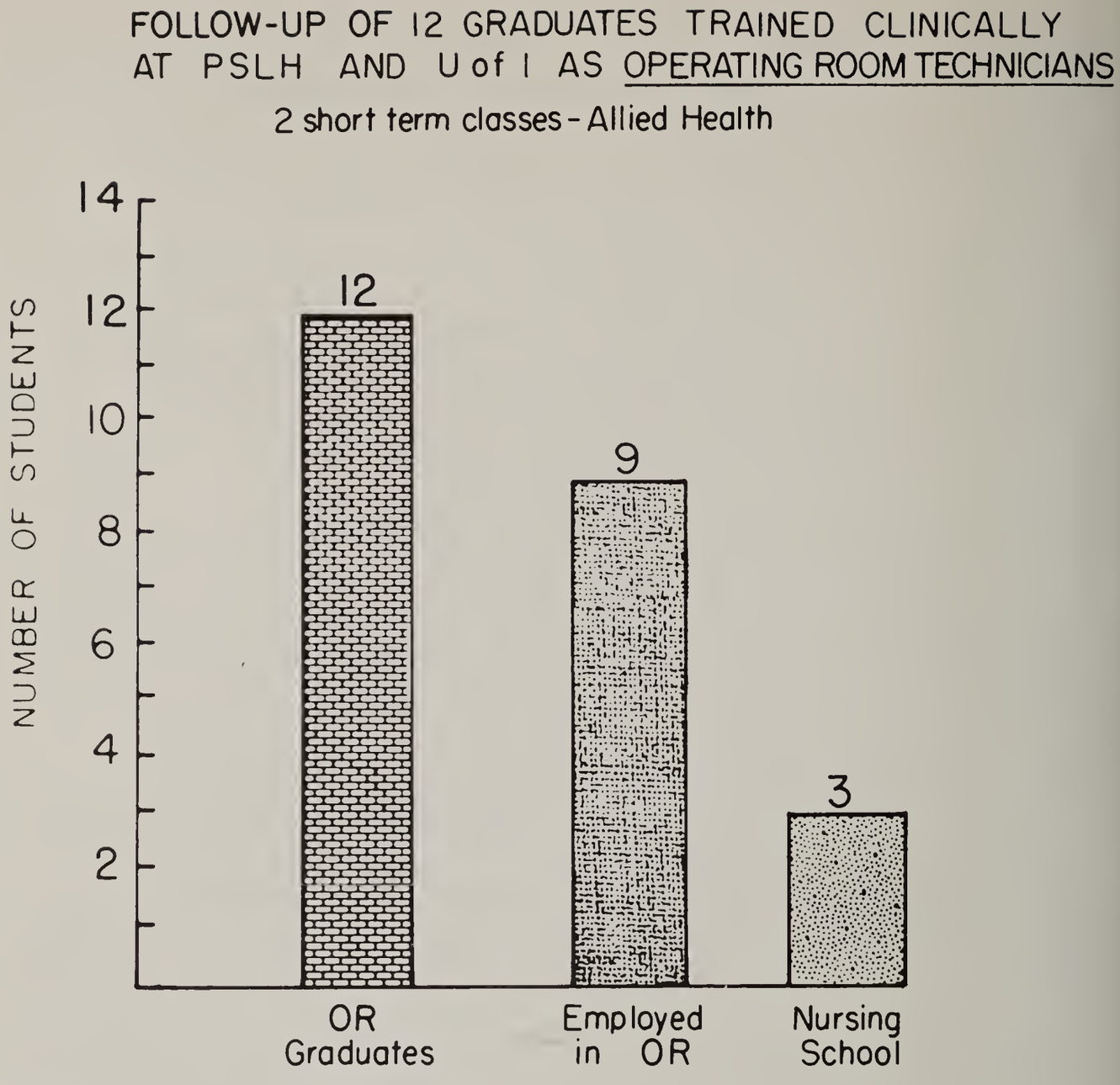

Fig. 1

individuals who withdrew during the program's first half did so because of financial problems, illness and for other "personal" reasons. Some left at either the didactic or clinical stage to go into other programs or employment.

The main thrust of this evaluation centers in the clinical training areas at Rush-Presbyterian-St. Luke's Medical Center. Some meaningful data are available on 190 participants who took their clinical training at this institution: 90 per cent of the trainees originally placed in clinical programs completed their training!

In four program areas—inhalation therapy aide, occupational therapy aide, psychiatric aide and unit clerk—clinical instructors had kept records that included students' educational background. No correlation was found between previous educational attainment and successful completion of a program.

It seems clear that other factors such as motivation, extent of personal involvement, and attitudes about the relevance of the program played an important part in the students' performance. A survey conducted by the community college on 60 graduates of the April, 1969 class indicated that the respondents rated the clinical portion higher than the didactic portion of their training (which however was also rated

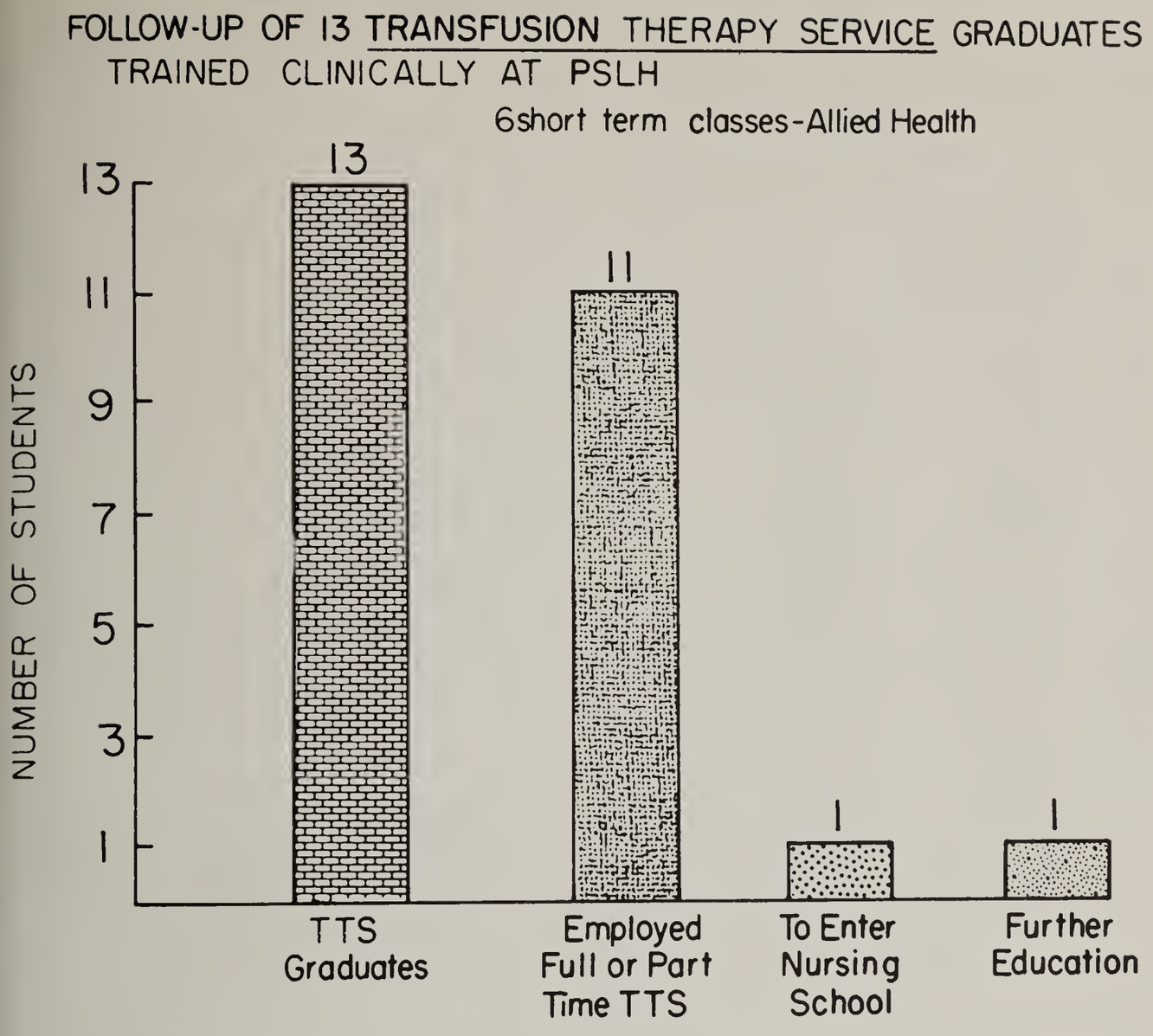

Fig. 2

relatively high). Program participants found their clinical instructors especially praiseworthy in their ability to make directions clear and understandable, their willingness to give personal guidance geared to a particular student's problems, and their desire to put students at ease in a work situation.

Figs. 1 through 4 are representative of what happened to 190 allied health students trained in ten different clinical areas at Rush-Presbyterian-St. Luke's Medical Center during 1968 and 1969. Three of these programs were conducted exclusively for the neighborhood health center affiliated with the hospital (community health aides, dental aides, mental health aides).

When results of these programs were viewed collectively, some striking patterns became evident. *First*, the majority of trainees who began the clinical programs, regardless of educational background, completed the course. *Second*, almost all of the program graduates were placed (found positions) in some health care facility. According to a recent count, 21 different hospitals accepted placements from the programs. *Third*, the highest proportion of graduates (60 per cent) was hired at the institution where they had received their clinical training (Rush-Presbyterian-St. Luke's Medical Center). *Fourth*, some of the individuals who entered the allied health field at this level have gone on to advanced training and higher status positions. Many particularly gratifying individual success stories can be cited. For example, some mothers whose support

FOLLOW-UP OF 63 STUDENTS GRADUATED AND TRAINED CLINICALLY AT PSLH AS INHALATION THERAPY AIDS

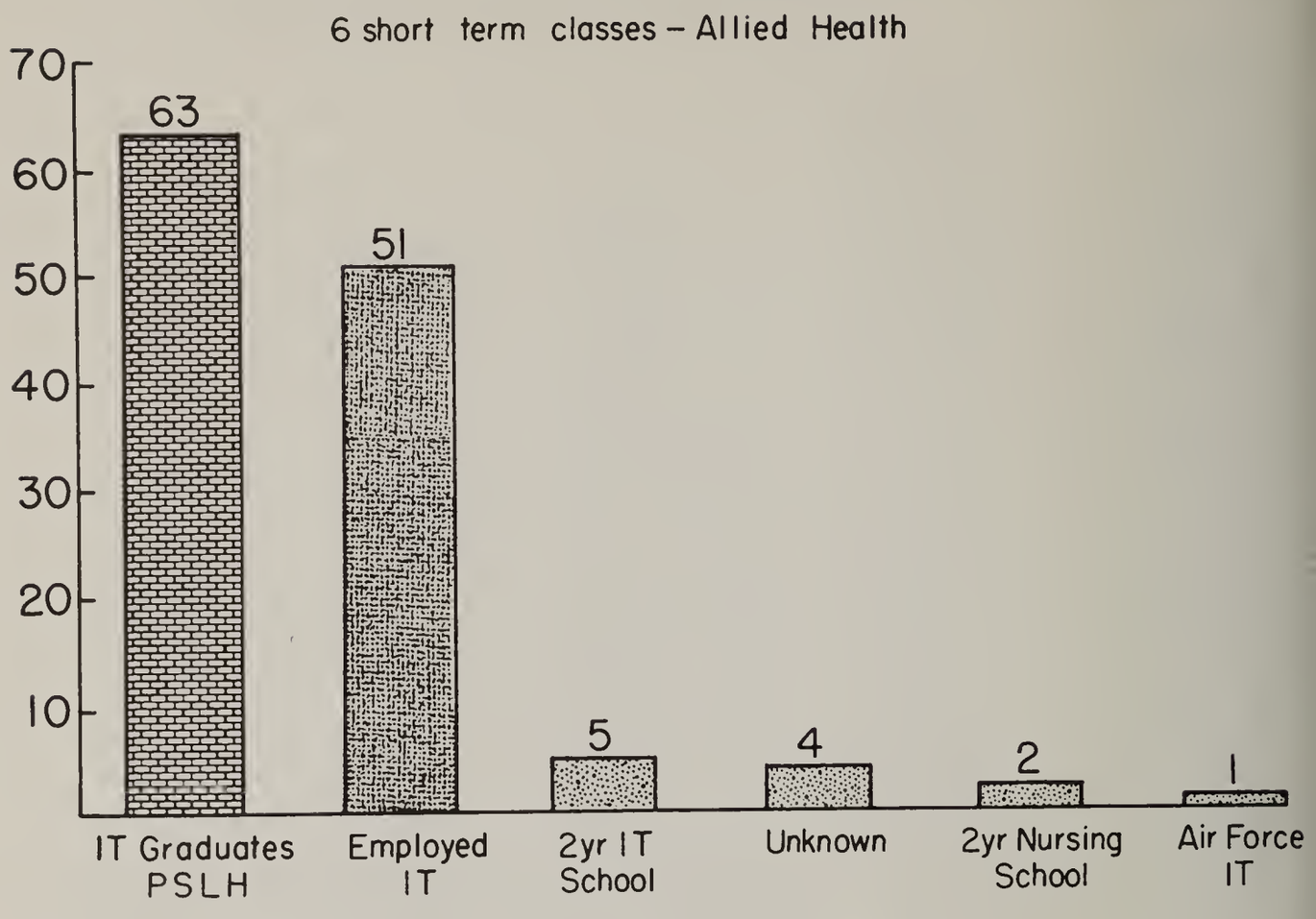

Fig. 3

came from Aid to Dependent Children (ADC) prior to and during matriculation went on to obtain their General Education Development (GED) certificates and then entered two year programs from which they graduated with Associate of Arts (AA) degrees. These individuals are now working at jobs requiring their new level of competence. Some program graduates have been involved in the initial organization of specialty departments in smaller hospitals. In more than one instance, entry-level graduates, after more advanced training, have actually become department directors or area supervisors at salaries which two or three years previously were beyond their expectations. *Fifth*, there is evidence that some individuals who dropped out of the program during the clinical training period re-entered and eventually graduated.

EFFECTS ON THE HEALTH MANPOWER MARKET

Although these preliminary results are quite encouraging from the standpoint of participant success, it should be emphasized that the full impact of such programs must be judged according to its effect on the health manpower job market. As the short-term pilot programs continued, several factors became apparent: first, program graduates soon began to fill most of the available entry-level positions in the metropolitan Chicago job market. Second, the development of more advanced programs designed to facilitate upward mobility to the next rung on the career ladder, was not proceeding at a rate fast enough to provide the kind of momentum necessary to keep the process going. Third, hospitals lacked uniform standards of requirements for entry-level jobs.

In other words, the market for entry-level jobs was becoming saturated, lack of new programs retarded the expected "upward push" to high level positions in many occupational categories, and placement of recent trainees was becoming more difficult because of varying hiring practices.

A survey of 51 metropolitan hospitals revealed that the majority of them still preferred to rely on their own in-service training programs to fill entry-level positions.[2] The most common explanation for this preference was a strong desire to have control over their programs thereby guaranteeing job specifications, position descriptions and salary ranges. Administrators and personnel directors from many of these institutions alluded to variations in their job standards ranging from basic terminology to actual duties and responsibilities.

Our own observation disclosed that there was relatively little communication pertaining to the allied health training programs among hospitals. We found a wide spread in starting salaries for the same position. Some institutions still continued to require a high school diploma from a program graduate even though this criterion had been waived by the community college.

DISCUSSION

In comparison to other training programs designed primarily for the unskilled, we believe this pilot project was a success. Since the aspect of training

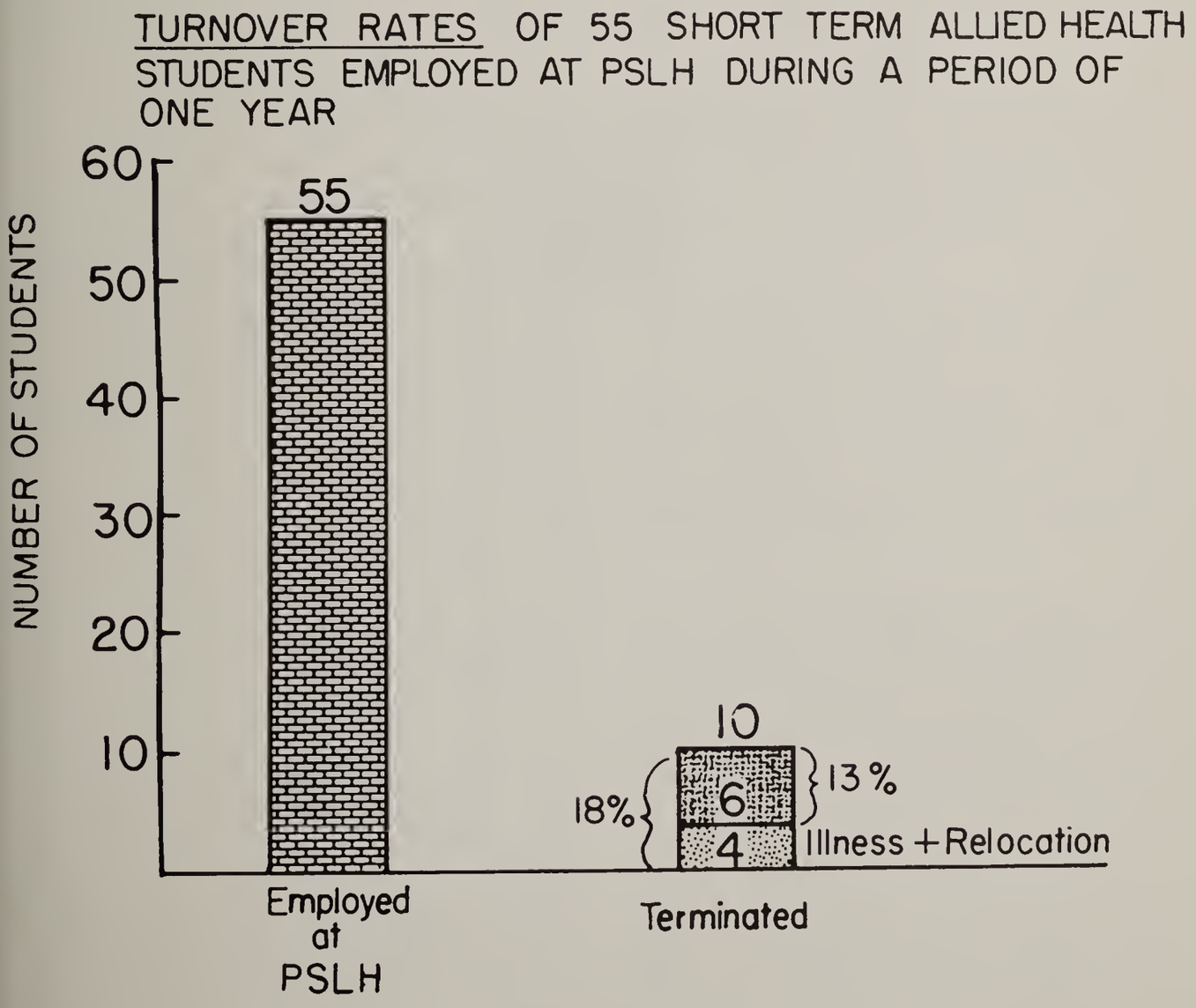

Fig. 4

with which we were most familiar was the clinical experience, most of our conclusions are based on observations in that area.

We believe that one reason the dropout rate was so low after students began their clinical traning was because they were placed in an actual work environment and required to perform real job-type assignments. Recent assessments of technical training programs have shown that the most successful (and also the programs considered to be most relevant by the participants) utilize simulated work situations.[3] One study[4] suggests that dropouts from the traditional (non-work oriented) programs tend to be abler trainees who leave because the program is too slow. They feel that if they are doing so well, they might as well leave and get a job!

There is a potential for a sense of fulfillment in work that simply cannot be duplicated in any classroom. Paul Goodman[5] speaks of "incidental education" as the only kind of education that suits the nature of learning. Probably the oldest and most established form of this kind of learning is the apprenticeship. This allows the individual the opportunity, as Goodman points out "to see real causes and effects rather than pedagogic exercises."

Through personal observations and discussions with instructors and students, it became more and more evident to us that our trainees were learning mostly by practice. A real work situation enabled them to develop a feeling of responsibility and personal accomplishment.

Benefits have accrued to trainees and also to health facilities. We are able to bring people with limited work experience into the health field, train them and subsequently see them employed. Further, in order to coordinate these programs it was necessary to bring diverse institutional representatives from administration, medical technology and health care delivery together for a common teaching goal. Finally, we were able to initiate new programs, including two-year associate degree courses, that have become a permanent part of our allied health training efforts.

At a time when it is common to stress the interdependence of medical and allied health education and the "health care team approach," we should not forget the entry-level of allied health training. For example, recently in our institution the nursing division and a group of physicians made an excellent video tape recording with respect to the right and wrong way of performing cardiac resuscitation. This training film put particular emphasis on the roles of *all* people involved in such an emergency including ward clerks, nurses aides, licensed practical nurses, registered nurses, physicians, inhalation therapists, etc. We believe it is this type of training approach which is important now and in the future.

Entry-level training through the community college or possibly through the high school may or may not be the proper answer to health care recruitment. Certainly the involvement of outside educational institutions at this level cannot occur to any significant extent until there is a standardization of job functions and salaries and until there is a comprehensive communication network between hospitals, educational institutions and other existing health occupation training programs. It may be that hospitals—teaching hospitals, in particular—should make an attempt to upgrade their in-service training programs by offering GED and basic educational courses to their employees, then encourage them to start their allied health career by enrolling in two-year Associate of Arts degree programs offered by the various community colleges. These programs could be in the fields of inhalation therapy, physical therapy, radiologic technology, two-year medical technology, two-year nursing programs, etc. Such an approach of course will not resolve all of the problems in this field today, for solutions to such problems as transferability of credit, ease of exit and reentry to training for progressively

higher level occupations,[6] and development of true career ladders starting at the ground level (not a "jungle gym" of intricate and often impossible paths) must be sought. However, it is a start.

SUMMARY

Several years ago Chicago City College and the Rush-Presbyterian-St. Luke's Medical Center cooperated in pilot programs to train allied health personnel. Previous reports have dealt with the structure of these programs. This article presents the available information with respect to student employment, upward mobility and some of the problems encountered with entry level training.

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PRELIMINARY STUDIES SHOWING USE OF AMNIOTIC FLUID CREATININE TO PREDICT FETAL MATURITY IN PREGNANT DIABETIC WOMEN

Gretajo Northrop
Vasil Truchly
Theodore B. Schwartz

INTRODUCTION

Successful termination of pregnancy with a healthy infant from a diabetic mother requires meticulous management of her diabetes, careful prenatal care, precise timing of her delivery to avoid the hazards of prematurity or stillbirth, and intensive observation of the baby by the pediatrician for early signs of post-delivery complications. Many clinical parameters frequently used to estimate fetal maturity cannot be employed in diabetic mothers. Baby size may be large or small for the gestation time, depending upon the management of the diabetes and/or the degree of vascular disease in the mother. The babies of diabetic mothers frequently respond to extra-uterine environment as if they were more immature than their size or gestation time would suggest. Recently Pitkin reported that creatinine concentration in amniotic fluid was useful in estimation of fetal maturity in normal pregnant women.[1] Only limited information is available on creatinine concentrations in the amniotic fluid obtained from diabetic women.[1-4] Preliminary studies relating amniotic fluid creatinine and its use in the management of diabetic gravidas are presented in this report.

From the Department of Medicine, Section of Endocrinology and Metabolism and the Department of Obstetrics and Gynecology, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois

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MATERIALS AND METHODS

Seventy-eight amniocenteses were performed without complications in pregnant women of whom 58 were diabetic as evaluated by oral glucose tolerance tests.[5] Careful abdominal examination to ascertain fetal positioning was followed by examination with a Magnaflux MD501 Ultrasonic Doppler Instrument to diminish the chance of a needle transversing an anteriorly located placenta. A four-inch Longdwel type needle was usually directed toward the area occupied by the fetal extremities to obtain approximately 5 ml of amniotic fluid. In some cases 1.5

to 2.0 microcuries of 125-Radioactive Iodinated Serum Albumin (125-RISA) and/or 400 mg of Sodium Aminohippurate (PAH) followed by 5 ml of Sodium Chloride Injection U.S.P. were inserted into the needle. The stylet was then replaced and the needle withdrawn approximately one-quarter inch, leaving the plastic extracatheter protruding beyond the needle. After 45 to 60 minutes a second sample of amniotic fluid was obtained and the needle was removed. Maternal blood pressure and fetal heart tones were monitored intermittently for 60 minutes. All patients receiving radioactive iodine were treated with 10 drops of Lugol's solution to prevent fetal and maternal thyroid uptake of any contaminating unbound ^{125}I.

To ascertain the accuracy of volume determinations performed in this way, known volumes of PAH and 125-RISA were delivered by plastic syringes into precisely known volumes of saline. Volumetric flasks were used to simulate amnions of known volume, and the concentrations of these agents were measured. PAH-concentration was determined by the method of Charles and Jacoby, and 125-RISA concentration was determined by measuring the radioactivity in aliquots of the 125-RISA used for injection, the amniotic fluid, the blood, and the urine, employing the same geometry in a Packard Tri-Carb Scintillation Spectrometer Model 3002.[6] Blood glucose concentrations were determined by an autoanalyzer method.[7] Creatinine concentrations in both maternal serum and amniotic fluid were also measured on the autoanalyzer.[8]

The estimated maximum dose of radiation sustained by the fetus following intraamniotic injections of 2 microcuries of 125-RISA is 0.13 millirads. The assumptions made and the calculations used in the estimation of fetal radiation are described in the Appendix.

RESULTS

To determine the magnitude of laboratory and mechanical error to be expected in measurement of amniotic fluid volumes, estimates by dilution technique of precisely known volumes were made (Table 1). There was no significant difference between the known volume and the volume estimates obtained by the dilution technique. In addition, estimates by PAH and 125-RISA gave essentially equal results.

Amniotic fluid volumes, determined simultaneously, using both PAH and 125-RISA in 18 patients are presented in Table 2. No significant difference was noted in the volume estimates between PAH and 125-RISA as performed in these patients.

Both creatinine concentration and the volume of amniotic fluid were determined in 37 patients; however a significant correlation between these parameters was not demonstrated (Fig. 1).

Highly significant positive correlation was demonstrated between both amniotic fluid creatinine concentration and gestation time (as determined by menstrual history) $r = +0.4730$ ($p < 0.001$). The difference between amniotic fluid creatinine and maternal serum creatinine concentration as related to gestation time $r = +0.4720$ ($p < 0.001$) in the 47 diabetic patients studied was also positively correlated (Fig. 2).

DISCUSSION

Prematurity resulting in neonatal death is a hazard which always accompanies iatrogenic alteration of gestation time. Because many intrauterine factors which adversely affect the babies of diabetic mothers are not understood and cannot be detected prior to fetal demise, preterm elective delivery is frequently performed in these patients in spite of the increased risk of prematurity. Recent reports of correlation of amniotic fluid creatinine concentration with fetal maturity in nondiabetic patients suggested that this test might also prove helpful in estimation of fetal maturity in diabetic mothers being considered for elective preterm delivery.[1,3,4,9,10]

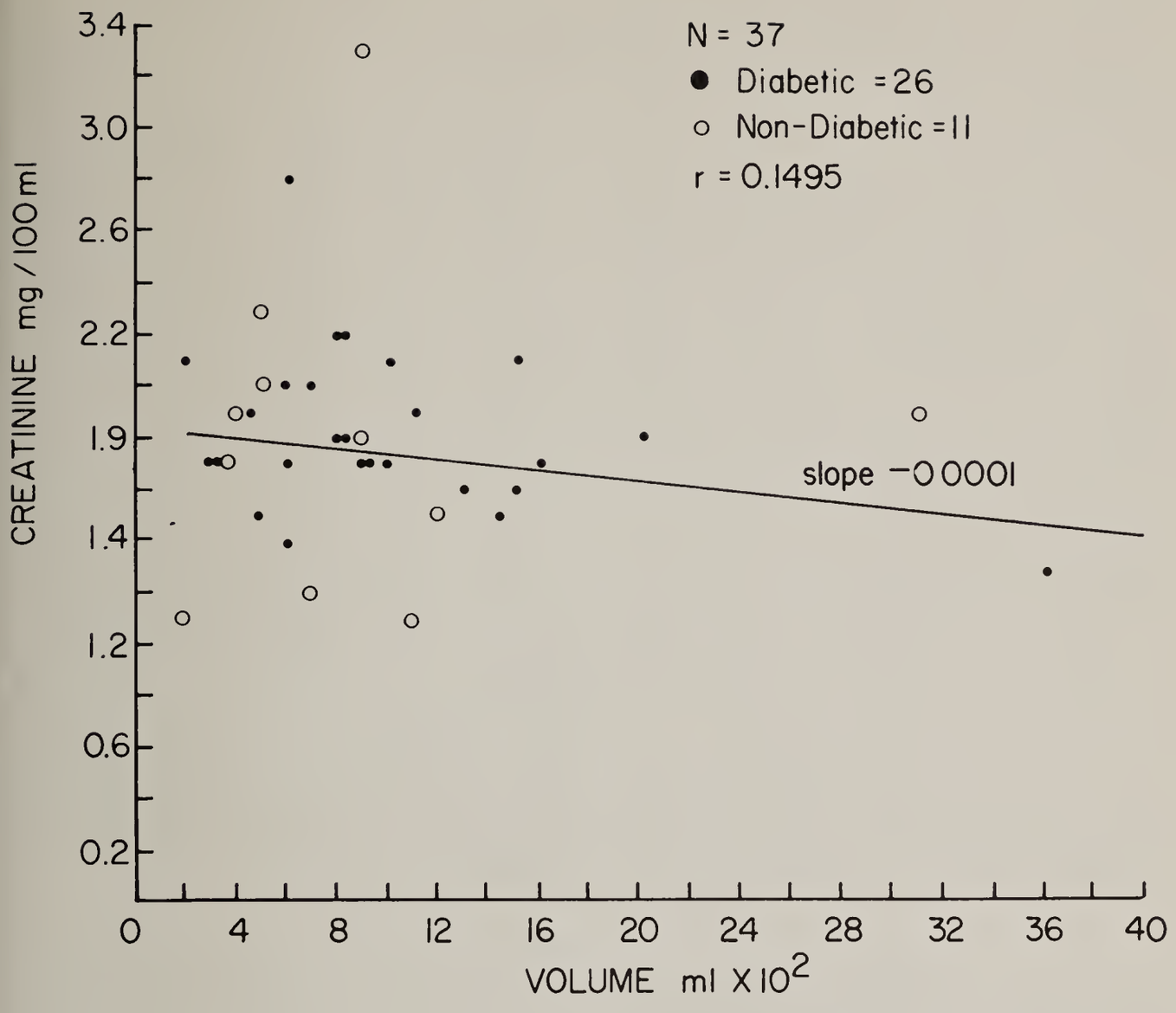

Fig. 1—The relationship between creatinine concentration and amniotic fluid volume in diabetic and non-diabetic patients.

Creatinine concentration in amniotic fluid and maternal serum are similar until about the 15th week of the gestation* followed by a gradual increase in amniotic fluid creatinine. About the 34th week a sharp increase in amniotic fluid creatinine concentration can be detected.[1] Suggested but unproven reasons for this increase include maturation of the fetal kidney with micturation or development of sufficient muscle mass to provide the biochemical precursor creatin.[9] Maturation of enzymes necessary for conversion of creatin to creatinine might be another likely possibility. Most investigators report that fetal maturity in normal pregnant women is probably adequate for extrauterine survival when the creatinine concentration in the amniotic fluid exceeds 1.5 to 2.0 mg per 100 ml.[1,3,4,9,10]

Anticipating that oligo-or polyhydraminos problems often encountered in diabetic mothers could influence the amniotic fluid creatinine concentration, volume determinations were made on the fluid contained in the amnion. Most of the information available on amniotic fluid volume has been obtained by dye dilution techniques employing Coomassi blue, an agent now banned in this coun-

*We have found creatinine concentrations in amniotic fluid and maternal serum in patients undergoing therapeutic abortion to be similar.

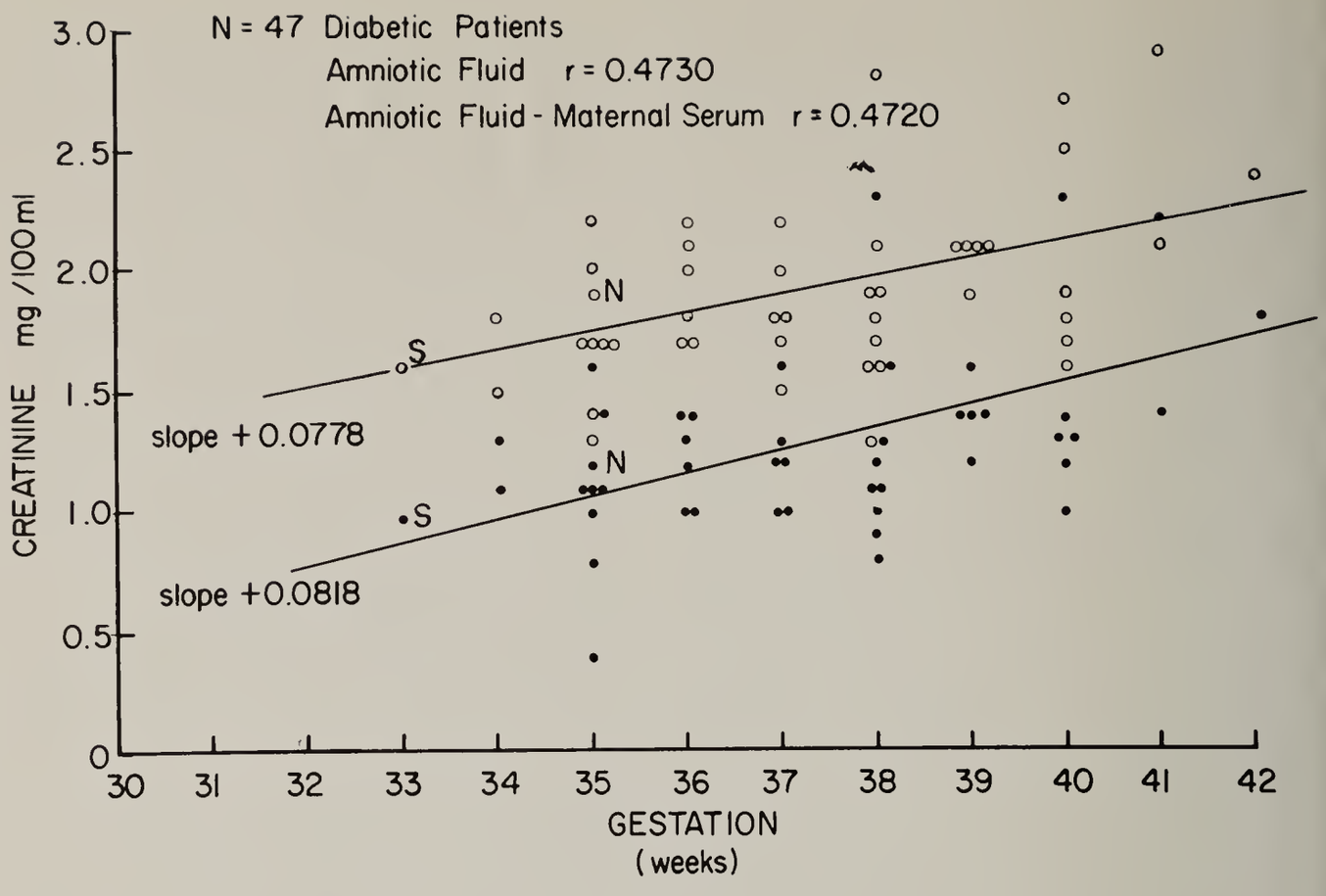

Fig. 2—The relationship between gestation time and (1) creatinine concentration in the amniotic fluid (slope + 0.0778), and (2) the difference in creatinine concentration between amniotic fluid and maternal serum (slope + 0.0818). *S* and *N* indicate stillborn and neonatal deaths, respectively. Both correlation coefficients are significant at the 0.1 per cent level.

try by the Food and Drug Administration.[11-14] PAH has been used for amniotic fluid volume determinations; however a special analytical procedure is required for quantitation, and this tends to preclude its routine clinical use. With careful administration of 125-RISA, excellent agreement in volume estimates, performed simultaneously using PAH and 125-RISA, was obtained (Table 1). Errors in amniotic fluid volume estimates using 125-RISA due to transport or binding processes appear unlikely as good agreement was obtained between volumes determined simultaneously in 18 patients with PAH and 125-RISA, agents which are biochemically and physiologically quite dissimilar (Table 2). The primary disadvantage in using 125-RISA for determination of amniotic fluid volume is radiation exposure to the mother and fetus. The maximum radiation dose to the fetus is estimated at 0.13 millirads. For comparison, the radiation dose sustained by the fetus following a single abdominal X-ray of the mother is estimated at 723 millirads.[15] It is emphasized that while any amount of radiation is believed to be a hazard, risks associated with 2 microcuries of 125-RISA appear to be more theoretical than real.

A clinical impression of the association of polyhydraminos with lower than expected creatinine concentration in the amniotic fluid was not supported. Correlation between creatinine concentration and amniotic fluid volume in these studies was not found. In addition, the total amount of creatinine present in the amnion as estimated from volume and concentration measurements was not related to the length of the gestation, to the weight of the baby, or to fetal maturity as clinically determined. A definitive explanation for the lack of correlation between the creatinine concentration and the amniotic fluid volume must await additional study of the biochemical and physiolog-

TABLE 1

Estimates of Known Volumes by PAH and 125-RISA

Volume Expected ml	Volume by PAH ml	Volume by 125-RISA ml
2000	1730	2102
2000	2160	1948
1000	1075	962
1000	975	967
1000	1020	967
1000	1163	961
1000	1053	978
500	549	510
500	510	522
500	526	528
500	540	525
500	573	544
250	277	264
250	302	257
250	276	253
250	344	264
Standard error of the mean:		
500 ml	10.9	5.1
1000 ml	29.2	2.8
Statistical evaluation by the paired t test between:		
Expected and PAH	$t = 1.50$	$p > 0.10$
Expected and 125-RISA	$t = -0.53$	$p > 0.10$
PAH and 125-RISA	$5 = 1.40$	$p > 0.10$

ical factors regulating volume and composition of this fluid.

Amniotic fluid creatinine concentration was found closely related to gestation time, as determined by menstrual history, in these diabetic mothers. It seemed possible that artificial elevation of the creatinine concentration in amniotic fluid could occur if maternal serum creatinine concentration was increased and thereby result in over-estimation of the gestation time. To avoid this risk the difference in creatinine concentration between amniotic fluid and maternal serum was used to estimate fetal maturity, as this value was also found to be closely correlated with gestation time. Thus, adequate fetal maturity to survive in an extrauterine environment is predicted when the creatinine concentration in the amniotic fluid is at least 1.7 mg per 100 ml (assuming a normal maternal serum creatinine of 0.6 or 0.7 mg per 100 ml) or when a minimal difference of 1.0 mg is found between amniotic fluid and maternal serum creatinine concentrations.

Amniotic fluid creatinine concentration was employed clinically in determining delivery time in 47 pregnant diabetic women. Forty-six mothers were delivered of living infants within seven days after the determination of creatinine. One infant was stillborn. Hypoglycemia was the only significant, however easily managed, neonatal complication until the closing days of this preliminary study. One infant weighing 3799 grams, delivered by Caesarean section from a Class D diabetic mother, died after three days, due to respiratory complications. Amniocentesis had revealed a creatinine concentration of 1.9 mg per 100 ml and maternal serum creatinine was reported as 0.8 mg per 100 ml, one week before delivery.

Although amniotic fluid creatinine concentration may relate to renal maturity in some as yet undefined way, the relationship of renal maturity to the development of other organ systems essential

TABLE 2

Simultaneous Estimations of Amniotic Fluid Volume by PAH and 125-RISA in 18 Patients

Gestation Weeks	PAH* Volume in ml	125-RISA* Volume in ml
35	888	871
36	2666	3124
36	392	313
40	1740	1511
38	940	1148
35	1818	2035
35	1818	1628
36	1290	1210
33	597	548
36	714	723
34	1053	1123
34	635	748
38	702	643
38	1428	1476
34	769	809
35	1428	1334
35	328	255
36	396	296

*No statistically significant difference between PAH and 125-RISA was found when the above data were evaluated by the paired t test, $t = 0.52$.

for extrauterine survival remains unclear. There is little doubt that knowledge of creatinine concentration in the amniotic fluid has offered an additional major safeguard against prematurity; however measurement of several constituents of this fluid may provide additional parameters upon which fetal maturity may be evaluated. For example, phospholipoid changes in amniotic fluid during the later weeks in the gestation period may reflect developmental processes occurring in the fetal lung.[16] Preliminary studies in this laboratory of sphingomyelin and lecithin ratios determined in amniotic fluid obtained from diabetic mothers may provide an additional parameter, an index of fetal lung maturity, with which to help assess fetal maturity. Prediction of fetal maturity may be expected to improve as additional parameters for estimating fetal development become known. It appears that when interruption of pregnancy seems indicated, evaluation of fetal maturity by a profile of studies which reflect the ability of essential fetal organ systems to meet extrauterine requirements may assist physicians in providing better "medical" care to the expectant mother and her baby.

SUMMARY

Seventy-eight amniocenteses were performed in 78 pregnant women 58 of whom were diabetic. Creatinine concentrations in the amniotic fluid and maternal serum were determined. Good correlation between amniotic fluid creatinine concentration and gestation time was found in these diabetic patients, thus corroborating other studies reported in non-diabetic women. Use of this information has successfully predicted adequate fetal maturity for extrauterine survival in 45 out of 47 diabetic patients in whom creatinine determinations were performed.

Similar estimates of amniotic fluid volume were obtained by dilution technique using both PAH and 125-RISA in 18 patients. Knowledge of amniotic fluid volume did not appear to be of additional help in predicting fetal maturity in the patients studied.

APPENDIX

Assumptions made in the calculation of the maximum radiation dose sustained by the fetus from intraamniotic administration of 2 microcuries of 125-RISA:

1. Uniform distribution of 125-RISA into a thick elipsoid phantom (the baby). This is probably valid as the baby swallows and excretes fluid constantly from and into the amnion. Excretion of radioactivity by the mother probably results from transplacental movement of 125-RISA previously absorbed from the gut of the fetus although transchorial movement cannot be ruled out.
2. Amniotic fluid volume is 1000 ml = 1 kg.
3. Fetal mass is 3 kg.
4. Effective half-life is four days as determined by subtracting the amount of radioactivity recovered in each 24-hour collection of maternal urine from that assumed to be present in the amnion (Fig. 3). Over 83 percent of the total radioactivity given to this same patient was recovered from the urine (Table 3). Similar recoveries were made in five additional patients. The following equation (top of page 73) was used to calculate the maximum radiation dose sustained by the fetus.[17]

TABLE 3

Summary of Recovery of Injected 125-RISA

SOURCE	PER CENT
Maternal Urine (12 Days)	83.1
Baby Urine (1 day)	0.7
Maternal Stool (12 days)	0.01
Maternal Blood (Not detected)	0.00
Amnion (Retained 125-RISA at Delivery)	2.2
Total Recovery	86.01
Unaccounted for 125-RISA	13.99
TOTAL 125-RISA Injected	100.00

Maximum Radiation Dose

$$D_{r(\infty)} = 3.07 \times T_{eff} \times \frac{q}{M} \times f \times E \times \phi \times \text{Back Scatter}$$

$$D_{r(\infty)} = 3.07 \times 4 \times \frac{2}{4000} \times 1 \times 0.063 \times 0.271 \times 1.24$$

$D_{r(\infty)} = 0.13$ millirads

T_{eff} = 4 days
q = 2 microcuries (125-RISA injected)
M = 400 gms (3000 gms fetus + 1000 gms fluid)
f = 1
E = 0.063
ϕ = 0.271 (uniform distribution of isotope into a mass of 4000 gms with a ke V of 60. (See Table IV)[17]
Back scatter = 1.24 (small mass, 4000 gms, located in the trunk of a 70-kg phantom. (See Table VI)[17]

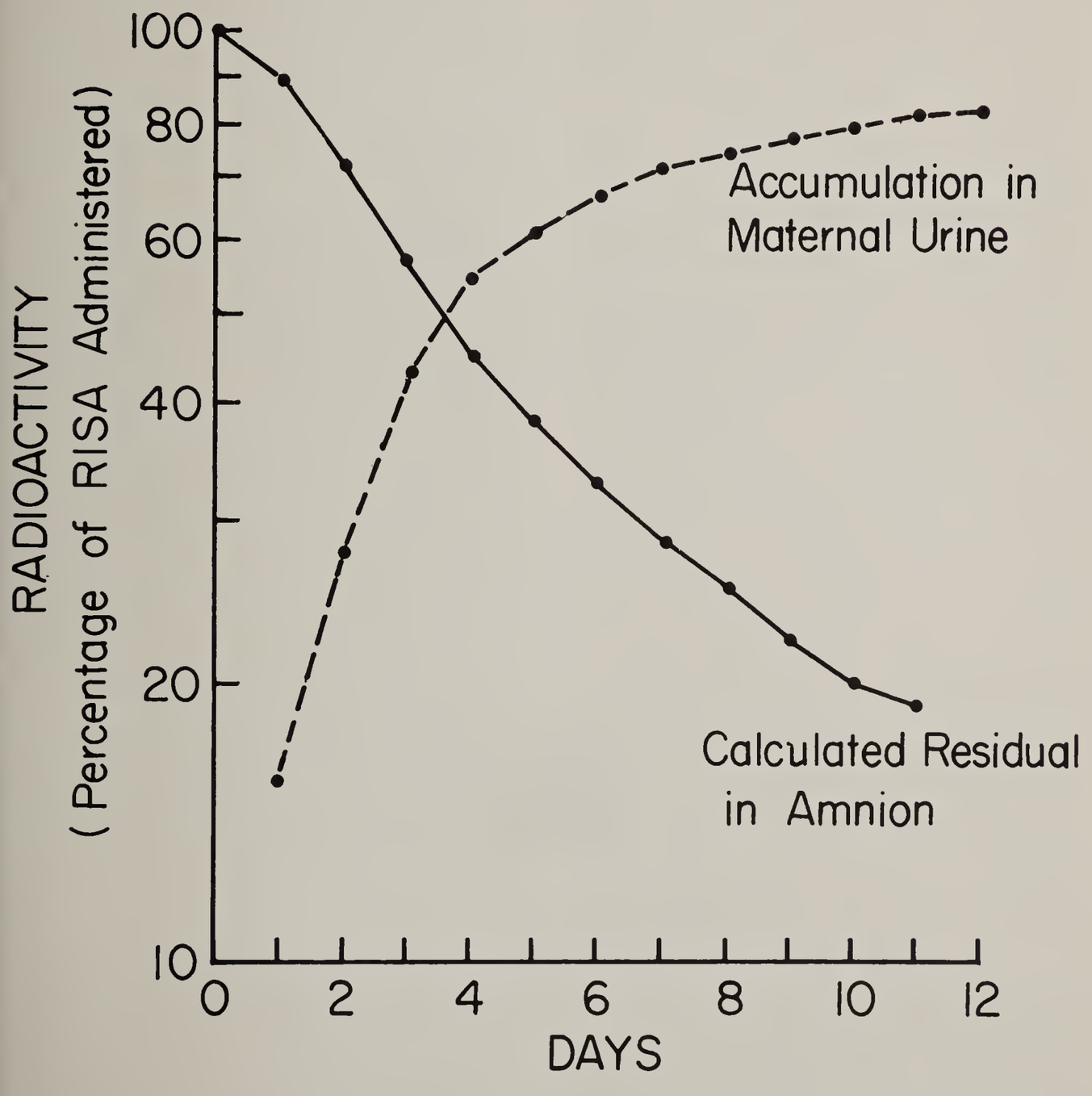

Fig. 3—Biological decay following intraamniotic injection of 2 microcuries of 125-RISA. Effective biological half life was calculated by subtracting the radioactivity accumulated in the urine each 24 hours from the known amount of radioactivity injected at zero time.

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THE MEANING OF HEALTH AND THE NATURE OF DISEASE

Geza De Takats

INTRODUCTION

From time immemorial man has struggled with the definition and recognition of health and disease. While there are often barely perceptible transitions between these two states, a truly sick person, an injured warrior or a drowning sailor has always attracted the attention of a group of people—who, by custom, decree, training, or compassion have concentrated on their care since the dawn of mankind. On the other hand, subtle transitions between health and disease are now being distinguished by trained observers daily and need to be recognized in order to be prevented or treated.

The State of Health

The human body is the sum total of a number of organs, supporting structures and regulatory mechanisms. A hierarchy keeps form and function in proper balance.[1] *Hierarchy* is an ugly word to a lot of people; it is loaded with ecclesiastic or military associations and conveys the impression of a rigid or authoritarian structure. Its correct symbol, however, in the state of health is not a rigid ladder but a living tree, a stratified, multi-levelled system branching into sub-systems. One may find this hierarchy even in the cell or in a defense reaction of the body against noxious stimuli establishing a priority of responses. *Teleology* is another principle, a concept that all natural processes serve a useful purpose. She is like a lady without whom no biologist can live, yet he hates to show himself with her in public (E. v. Brücke, 1896). Teleology tries to maintain, through regulatory forces and feedback mechanisms, a stable internal environment, beneficial to the interests of the human body.

For example, if the blood sugar rises following a carbohydrate meal, the pancreas ejects insulin to lower blood sugar. When this mechanism is inadequate or exhausted, diabetes results. This statement is, of course, an oversimplification of a complicated regulatory function but illustrates the point of a failed response to a daily-occurring stimulus. There is a good chance that implantable plastic models may substitute in the future for such defective organs.

There are a large number of other teleologic mechanisms. *Homeostasis* is a purposeful mechanism maintaining an equilibrium of functions, chemical composition of fluids and tissues and counteracting any external or internal influence which menaces the steady state. Subtle disturbances of this mechanism might be responsible for many manifestations of ageing.

Thus we can arrive at a simple and reasonable definition of the state of health: it is a balanced internal environment—the "milieu intérieur" of Claude Bernard—which is maintained in the face of noxious or stressful impulses from the

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An address presented to the first class of freshmen, Rush Medical College, Chicago, Illinois, 1971

outside and inadequate regulatory functions from within the body.

This is truly an old concept, formulated among others by John Brown, a Scottish physician, who urged the doctors in 1776 not to overemphasize clinical symptoms, like the French have, but to investigate external agents which consume the "excitability" of the body. For him, the symptoms and signs of disease are only effects of the imbalance and are not of primary importance.[2]

To paraphrase this dictum into modern verbiage: when you concentrate on risk factors known to facilitate heart attacks, and measure heart rate, blood pressure, weight, blood fat and number of cigarettes consumed, you are measuring not the causes but the effects of insecurity, greed, ambition, competition, heavy traffic, air and noise pollution and their effect on genes, molecules and cells which may not respond adequately. The study of such stress factors, seems more important than nibbling at their sequelae. The story is that of the chicken or the egg. Which came first? The behavioral scientist has much to offer by breaking down the elusive concept: stress, into components which can be measured in a reproducible way. Perhaps the high blood uric acid found in gout is the cause and not the consequence of ambition.

The Nature of Disease

I have already hinted at the obvious expansion of the concept of health from being a well-functioning equilibrium, to a failed adaptation to external and internal stimuli. The Greek concept of health as harmony between man's nature and external environment derived its validity from observable effects of sudden changes in weather, food and way of life, causing insults to man's well being. About 500 years before Christ, the Golden Age of Greek medicine began to sever its direct connection with religion and its control by the priesthood. On the Island of Cos, a health resort, medical school and hospital, the Medical Center of today, Hippocrates was born. He taught direct observation and the study of the onset, course and outcome of disease. A considerable portion of his writings is certainly not his own but "Airs, Waters and Places" seems to have real authenticity.[3] This treatise clearly emphasized the role of environment on the characteristics of man and boldly suggested that climate, topography, soil, food and water affect not only the health and temperament of national groups but their social institutions and even their military prowess. According to Hippocrates, the human organism is literally a "cosmic resonator," responding with varying intensity to every change in the meteorologic environment.

If you read this treatise, which was reprinted for use in German medical schools as late as 1874, you will find that Hippocrates also recognized another important factor in the development of disease, namely the reactivity of the individual to various forms of stimuli, be they emotional or physical.

At the end of the last century, however, the natural sciences introduced two components which seemed to make hippocratic medicine obsolete.[4] One was the doctrine of specific cause and effect. Tuberculosis was not caused by a damp, cold basement but by the tubercle bacillus. Typhoid fever, suspected to be brought on by stagnant water or a rotten egg, was caused by Salmonella typhi. The second trend consisted of widespread interest in the individual structures and mechanisms of the human body. Correlations of form and function were described. The light microscope, which became the proud possession of every medical student, was expanded to the electron microscope opening up vistas of previously only imagined or postulated structures like viral particles and permeable cell membranes providing a magnification up to 60,000.

Functional studies of individual organs under basal or stressful conditions provided another post-hippocratic trend in the evaluation of disease. A vast array of laboratory procedures developed, creating bottle necks of manpower, mostly woman power, gradually dominated by

computers, autoanalyzers, biostatisticians and mathematical biologists. Profiles of organ function of heart, liver, kidney and blood appeared, adding masses of data, sometimes indigestible or undigested. In this post-hippocratic era, the deeper the bioscientist delved into the batteries of statistical data, the farther away he got from the person, from the *host* in whom the *disease* occurs causing his *illness*.[5]

The Neo-hippocratic Era

Thus the stage was set for a new look, in which the clinician, no matter how deeply steeped in basic science, did not want to be dehumanized, did not want to become an automaton, an apparatus at the bedside. He felt an urgent need for a restudy of the responses of the whole integrated human body to external stimuli and to the adaptive potentials against internal derangement, directing, but not directed by the laboratory.

This, now, is the true neo-hippocratic phase which is a rebound phenomenon from the post-hippocratic era, still rampant in some quarters. Simple accumulation of mass statistics, batteries of ill-digested data have diverted the student of medicine from the patient who, indeed, should have the benefit of the latest technology, but who primarily wants and needs care. Unhampered pursuit of basic research without being forced into the procrustean framework of "part-time project research" needs full support and adequate funding. The part-time categorical research, from which practical results are expected even before the grant expires, is often a waste of time and moreover a waste of precious manpower. The high-powered laboratory man who becomes the head of a large clinical department, would perform better in the laboratory and cannot adequately teach and cope with patient care. He may well become a voracious grant-eater, spending the taxpayer's money and diverting promising future clinicians from their primary function.

As Henry Miller pointed out,[6] concentration on the laboratory makes it easy to forget that medical research is essentially directed toward human need and has a social function beyond the mere satisfaction of the investigator's curiosity. Progressive educators recognize that the hierarchical distinction between pure and applied science is an anachronism. The activities of a clinician often pay an unexpected dividend in basic knowledge. The renal physician has taught us more about the function of the human kidney than the physiologist—the transplantation units have given modern immunology a great forward push. The relationship between basic and clinical research is that between discovery and invention. Fleming discovered penicillin. Florey invented it.[6]

Three important fields of medicine have opened up in the neo-hippocratic era: biophysics, genetics and immunobiology, although traces of such trends have surfaced in the past from time to time. Inevitably with all the flow measurements, pressure determinations, isotope scanning and others, the importance of physics applied to medicine has to be stressed. There is always the danger that in the effort to quantitate statistically valid data, this physical and mathematical biology may suppress or deflect true clinical judgment. Properly harnessed and put in its proper perspective this field has vastly contributed to the understanding and management of disease. The importance of the genetic component in almost all diseases has become obvious. There is a continuous spectrum from illness almost entirely determined by the individual's genetic constitution to those almost entirely dependent on environmental influence. In between are a large second group like congenital dislocation of the hip or duodenal ulcer, in which genetic factors and environmental experiences each make a substantial contribution to the disease process.

Genetic counselling is indeed true preventive medicine. It may become as beneficial or as destructive as any pharmacologic or surgical therapy. The responsibility of the geneticist, who may fertilize

the semen in the test tube and be able to produce one hundred Hitlers or one hundred Einsteins in a glass container followed by implantation into a proxy mother's uterus is more awesome than the responsibility of those who produced the atom bomb.

One is reminded of Aldous Huxley's *Brave New World*, in which elevator men are produced by selective breeding, who have neither the capacity nor the desire to do anything more than open the door of the elevator and exclaim, "What a beautiful day!" Such experiments of selective breeding, while leading only to marginal benefit may cause social problems.

The third field of inquiry into mechanisms of disease processes is *immunobiology*. Immunity is usually meant to be synonymous with resistance not only to infectious agents but to foreign particles, toxins, living cells and cancer. Its success is based on the ability of living organisms to recognize foreign molecules unrelated to their own normal structure. Immunity may be acquired as a result of prior experience with a foreign substance or it may be nonspecific in which case it is genetically determined. The success of organ transplantation is really based on the management or suppression of resistance to the foreign material; the surgical problem is more or less in the bag.

The Delivery of Health Care

It seems useless to study and teach medicine unless one knows how to deliver it to the maximum number of people. There are a variety of private and governmental agencies seeking for the solution to treating not only people but whole communities. Only recently—notably since the Coggeshall report in 1965—have medical schools begun to examine the methods available to keep the population at large in good health and to administer to the sick when they need it.

While this huge and important problem is not our immediate concern it would be, indeed, a sterile exercise if our accumulated knowledge could not be properly and evenly distributed to the public. The cost and delivery of health care needs to be examined as rigorously as other areas of medical and biological research and such studies need to be introduced into medical schools.

It is customary today to speak condescendingly of the old, non-system of *cottage industry* based on private physicians, small community hospitals and nursing homes. As one who practiced in this era, I am the first to admit that this system is now archaic. It was good while it lasted.

With the advent of giant industrial complexes, supermarkets and skyscrapers the health industry had to move in the same direction. Health planners have developed empires to render community service requiring considerable federal and state funds, and weaving a network of affiliated hospitals with allied medical science projects.

Whether this Tower-medicine administered by a galaxy of interlocking agencies is going to be more effective in establishing the *need* of the sick and separating it from the demands of the "worried well" is yet to be shown. Desirable as the goal may be to provide the ultimate in medical care to every citizen, our present available resources, personnel and material are yet inadequate for the task.[8] Also the object of medical care, formerly the patient, and now the community, begins to demand participation and directing influence in their health care. This is not unlike the belligerent patient in our office demanding to control and arguing the merits and costs of his medical care, except the voice is multiplied by one half to one million.

This Megamedicine of Megalopolis is part of the present trend. The skyscrapers get taller and the supermarkets have squeezed out the small grocer but as the renowned architect and town planner, Doxiades, has pointed out, these superstructures may die out like the dinosaurs did when their frame got too big for their guts. Recognizing the ancient law of action followed by reaction, relatively small group clinics, providing prepaid care and affiliated with a neighboring

teaching center could conceivably emerge from an overcentralized and overadministered Supercare.

In our period of transition and ferment one may observe a number of extremes and paradoxes. Here is the old country doctor compassionately holding the hand of his dying patient—at home—instead of treating him in the intensive care unit of a well-equipped hospital. On the other hand, observe the ambitious resident of a large hospital unit, demanding a battery of irrelevant, costly and sometimes hazardous tests in a patient whose wife deserted him for an itinerant jazz musician. And here is the human Megamachine, the mass-man, totally adjusted to his environment and accepting repairs from a pool of interchangeable technologists who keep computerized records and whose automated response to a defective machinery is predictable and uniform. All systems go, the computers compute and the autoanalyzers analyze.

And how will the patient feel about all this? It is quite likely that his personal physician—selected because he has offices above the friendly druggist or because he is such a fine fishing or golfing companion —has greater deficiencies on the average than those of an adequately-programmed computer; but will he like to be diagnosed and treated by a machine? Only, in my opinion, if he has become a machine himself.

Computing science has, indeed, revolutionized such functions as scheduling of hospital admissions, keeping of medical records and operations of the laboratory, pharmacy and intensive care unit. This is an obvious forward step. The question is: will the computer really relieve the shortage of physicians, improve the quality of medical care and make the doctor an ultimate decision maker? Will it not only interpret the electrocardiogram and automate the taking of history, but will it become a consultant? Will it deliver anesthesia, will it evaluate the physician's performance to his peers and possibly to the hospital administrator and thus become an "electric snooper"?

Conceivably a centralized form control of information sources can be devised[9] with only a single type of program available for each medical problem, thus eliminating diversity, flexibility and differences of opinion, which are the exciting challenges of present-day medical management.

There is the frequent assertion that all the massive diagnostic hardware will simply enhance personalized medicine by freeing the physician from donkey-work. One can be highly skeptical about this hope. If one has analyzers to do thousands of tests daily, one will have other machines to print-out, distribute and eventually interpret these tests. Thus humans today may become personnel tomorrow.[10]

The development of a fully-automated diagnostic and therapeutic service to the patient is, indeed, quite feasible. If the world around us has changed to accept this system, obviously food services, legal procedures, engineering products and even compatible marriages will have to be computerized. If this truly happens, let the Mars Men or the chimps take over.

There is the other end of the spectrum: Witch-doctors, faith-healers and quacks of many denominations have a potent weapon in their hands, especially if organized medicine ignores them. Approximately thirty per cent of patients whose diagnoses include terminal cancer, heart disease or stroke can be relieved of pain—at least temporarily—by a proper psychologic approach which the computer is just beginning to understand. In countries where medicine veers away from the individual care, the naprapath, the chiropractor and the voodoo man flourish.

The need for a humane personal approach is obvious to all health planners. They pay lip service to the right of everyone to obtain optimal medical care and then go on to plan a system that revolves around massive technology and life-threatening emergency care.[10] The use and abuse of technology is seemingly running wild. In one of the Boston hospitals, the number of laboratory tests jumped from 381,088 to 520,670, an in-

crease of more than 36 per cent between 1968 and 1969. In another recent survey from the University of Rochester, laboratory tests made up 25 per cent of the total hospital bill, the house staff ordering too many tests repeated too often. Mass screening procedures, more and more popular as fund raising projects for voluntary health agencies, generate a plethora of salaried jobs and non-disease.

In this maelstrom of opposing trends and social improvements the figure of the "compleat physician" stands out all the more clearly. He understands technology, has mastered it, but is not run by it. He knows the effect of mind on the body but does not believe that every swallowed chicken bone is psychosomatic. He may work alone, in a group, or in a regional setup, he may be salaried or he may prefer fee for service. His integrity and his ever-expanding knowledge promptly applied to the patient are what really counts.

Epilogue

Inevitably the practice of medicine reflects its environment and the cultural trends of the people it serves. The impersonal nature of the crowd culture, the high-rise apartment, the crowded street and the packed elevators only accentuate the isolation of the individual and may create hostility. A constant malaise in American life today is depersonalization and it cannot help but transmit itself into the field of medicine.

In addition, there is strong desire to transmit basic knowledge as quickly as possible from ivory towers to the man in the field. Mass media pour out unfinished research to the public. It has been said that scientific discovery moves in a kind of natural cycle.[11] First there are the sowers, who lay down the basis of the subject; then the reapers, who gather the great bulk of the harvest of knowledge; after them come the gleaners and finally a few geese who peck at the remains. Sir MacFarlane Burnet, the eminent biologist, has suggested that medicine itself may be moving into the latter stages of this cycle. Thus from a hippocratic, post-hippocratic and neo-hippocratic phase we may have arrived into the age of geese.

It will be up to you to select the area of medicine you wish to cultivate and how you want to deliver it. It is surely the purpose of your studies to get a balanced view of the subject and to open new horizons. The view from the top will be spectacular. The toil up the ladder is hard, often discouraging, but the reward is great. Scatter the geese and start sowing the new seeds.

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MILE SQUARE NEIGHBORHOOD HEALTH CENTER—AN OVERVIEW

Joyce C. Lashof

INTRODUCTION

The Economic Opportunity Act of 1964, commonly referred to as the war on poverty act, was enacted on August 20, 1964, to strengthen, supplement, and coordinate efforts to eliminate poverty in the United States. The Act authorized the establishment of various programs intended to open to everyone the opportunity for education and training, the opportunity to work, and the opportunity to live in decency and dignity.[1]

Title II of the Economic Opportunity Act, as amended, provides for the establishment of Community Action Programs (CAPs) designed to provide stimulation and incentive for urban and rural communities to mobilize their resources to combat poverty. These programs are to be focused upon the needs of low-income individuals and families and are to be developed, conducted, and administered by public and private nonprofit agencies, with maximum feasible participation of residents of the areas and members of the groups served.[1]

The Comprehensive Health Services Program, of which Mile Square Health Center is a part, was authorized as a specific component of the Community Action Program by the 1966 amendments to the Economic Opportunity Act. In specifically authorizing the Comprehensive Health Service Program, these amendments expanded and broadened the concept of the neighborhood health center, which had been developed by the Office of Economic Opportunity (OEO) in 1965 and early 1966. They authorized the Director of OEO to contract, or provide financial assistance, for the development and implementation of Comprehensive Health Service programs focused upon the needs of persons residing in urban or rural areas having high concentrations of poverty and marked inadequacy of health services.[1]

Historical Background

The Mile Square Health Center is one of the original eight health centers funded by the OEO and was established by a grant awarded to the Chicago Health Research Foundation in July of 1966. The delegate and sponsoring agency is Presbyterian-St. Luke's Hospital, a teaching hospital then affiliated with the University of Illinois, now with Rush Medical College, in Chicago. The comprehensive health care program being carried out by the Mile Square Health Center was developed by the Section of Community Medicine of Presbyterian-St. Luke's Hospital in 1966, and the Center opened its doors for service in February, 1967.

The Center is located about in the middle of a one-square-mile target area which, according to the 1960 census, had a population of about 30,000. The target area is situated in one of the 24 areas

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identified by the Chicago Committee on Urban Opportunity as areas of concentrated poverty. The area is further identified as one of the four areas in Chicago with the greatest concentration of poverty. It is approximately 90 per cent Black, 5 per cent Puerto Rican, and 5 per cent white.

The 1960 census indicates the median income within the target area as approximately $3,400; the male unemployment rate was approximately 13.6 per cent. Thirty-three per cent of the people live in public housing projects, and slightly more than 40 per cent of the families in public housing, and 25 per cent of the residents of other housing receive welfare assistance. Of the families in the public housing projects, 55 per cent are categorized as broken families (generally only a mother in the home).

The usual mortality and morbidity statistics would indicate that this community is among those with the lowest health record.[2]

Affiliation and Coordination

Technically, Mile Square Health Center operates under authority delegated by the Chicago Health Research Foundation, a research arm of the Chicago Board of Health. While the Foundation exercises no authority over the clinic operation it does oversee the execution of the clinic's contract and insures that there are adequate financial controls as well as providing a resource for technical and program assistance when needed.

The health programs of the Chicago Board of Health are closely coordinated with those of the neighborhood Health Center, with referrals being made to the Center by the Board of Health for all eligible persons in the target area. Working relationships have been developed between other health care providers, social service agencies, and Headstart programs within the general area. In addition, close contact has been developed between the nursing and the social service departments of the neighborhood Health Center and the office of the Cook County Department of Public Aid, so that resources of both programs can be utilized for the benefit of the participant.

Issues Associated with the Foundation of the Plan

The following problem areas were confronted in the development of the Mile Square Neighborhood Health Center and, by analogy, apply to the development of most neighborhood health centers with a high degree of community participation involved in their development and operation.

The major problem facing medicine in the urban community today is the development of an organized approach to the delivery of medical care to large groups. The challenge is to develop a system by which all members of the health profession can be brought together with the community to provide comprehensive health services for the population.[3] Before this can be done, the present level of health care in the community, the present availability of medical resources, the patterns of utilization of these resources, and general demographic data must be obtained. Studies to determine this information were undertaken in the initial phases of the development of the Mile Square program, and the results were instrumental in setting its direction and emphasis.

The organizers of the Health Center felt that community involvement and even a degree of control were essential in making the health services responsive to the desires and needs of the community. There was also clear recognition of the value of the OEO's requirement for "maximum feasible community participation."

The question of "who represents the community?" had to be addressed. The solution is not an easy one. Communication between the various groups within the community was hampered by racial and cultural barriers as well as by differing attitudes as to what was needed and by what method it should be acquired. All the interested groups in the community, organized and unorganized, militant and nonmilitant, professional

and nonprofessional, had to be represented. Recruitment from the community, both in the selection of the initial advisory committee and in developing an active community board, as well as staff personnel, was and is a continuing problem.

The development of Mile Square Neighborhood Health Center required the cultivation of working relationships with multiple and diverse departments of its own sponsoring organization, Presbyterian-St. Luke's Hospital, as well as with other city, state and federal health organizations. State and city agencies were dealt with in arranging funding from welfare and Medicaid sources. The Center's contact with the federal government has been almost entirely with the OEO, upon which the Center is dependent for funding. Funding is on a yearly basis, with reports on utilization and costs being submitted quarterly. Refunding proposals must be submitted annually.

An additional concern has been the obtaining of adequate funds so as to enable all of the patients cared for at the Center and in need of hospital care to be hospitalized at Presbyterian-St. Luke's Hospital.

Finally, a major problem facing the Center has been the lack of adequate space in which to carry out the total program in an efficient manner. The Center program was opened in an old brownstone building which was renovated as a temporary center. Efforts to obtain funds for a new building were initiated early in 1968. Building plans and funding mechanism for a new health center have finally been completed, and ground-breaking for a new Center is expected in October, 1971.

Involvement of Area Residents in Policymaking and Conduct of the Center

The Economic Opportunity Act, as amended, provides that neighborhood-based organizations composed of residents of the area or members of groups served by the project, should be encouraged to assist in certain activities related to the project.[1] OEO health program guidelines further provide that residents should have a substantial voice in policymaking, should be selected democratically from the residents of the community, and generally should be involved in such activities as review of applications for OEO assistance, the establishment of program priorities, the selection of the project director, the fixing of the location and the hours of the Center's operation, the selection of staff personnel, the development of eligibility criteria and fee schedules, and the evaluation of suggestions and complaints from the community.

In keeping with these recommendations, the neighborhood Health Center Advisory Board was established at the inception of the program and has reviewed all grants, policies and program content and has contributed to all decisions concerning the matters listed in the previous paragraph. No new programs may be introduced without prior approval of the advisory board. The advisory board helps to plan and review the budget, as well as develop the eligibility criteria and priorities of the program. Ninety-eight per cent of all members of the advisory board live within the Mile Square community and were initially selected by block clubs and tenant councils.

Recruitment and training of the clinic staff are joint responsibilities of the Health Center and the community board. In experimenting with new and innovative ways to deliver medical care, and in the face of the current scarcity of professional manpower, the clinic has focused attention on employing and training community residents. Area residents have been trained as community health aids, mental health workers, and youth workers.

The community board is now structuring itself to form a community corporation that can assume full responsibility for the administration of the program and be the grantee.

Objectives

The specific objectives of the Health Center program are: to provide continuous family-centered, comprehensive medical, dental and mental health care to the residents of the Mile Square community; to increase the application of existing knowledge and techniques of medical care at the community level, and to develop new knowledge relevant to the care of poor families in a community setting; to evaluate the use of specifically-trained individuals in providing certain aspects of comprehensive medical care, with special emphasis on the cultural and socio-economic problems as they affect health care; to give physicians, dentists and paramedical personnel insights into their potential role in, and responsibility for, bringing medical and dental knowledge and skill to the community; to evaluate the appropriateness of the present functions of health workers, and to determine new roles by which they can provide care; to explore similarly how much specifically-trained lay people can extend the services of the professional cadre.[4]

Scope of Services

Medical service is provided through three echelons of care. The first is represented by the public health nurse and community health aide who function primarily in the home. The second echelon is the Center itself, where a core of internists, pediatricians, obstetricians-gynecologists, and psychiatrists and a supporting nursing and social work staff provide the usual office practice care. The third echelon is the hospital, its specialty clinics, surgical facilities, and inpatient care.[3]

The total services in all aspects of the program are available to each patient. Referrals between departments may be initiated freely, and all patients are informed of the total scope of the program. (For example, any patient attending the adult medicine or pediatrics clinic is referred for dental care as indicated, and vice versa, any patient seeking dental care is referred to the appropriate medical department for medical checkup prior to dental treatment, except for acute dental problems.

The neighborhood Center is open from 8:00 a.m. to 9:00 p.m. Monday through Friday, and 8:00 a.m. to 1:00 p.m. on Saturday. At all other hours care is given at the emergency room of Presbyterian-St. Luke's Hospital, and patients are informed of the availability of this service. Additional services are provided either in the home—by the community health field team (public health nurses and aides), by physicians when absolutely necessary, and at Presbyterian-St. Luke's Hospital for all specialty services and inpatient care. A 24-hour telephone answering service is available, staffed by a nurse, with physician back-up.

All patients are assigned to a primary physician, a family dentist, and a community health nursing team who are responsible for the totality of care. Only in an emergency or an acute illness necessitating a visit at a time when the patient's own physician is not in is he seen by other members of the staff. Patients have the right to change their physician if they so desire.

The Medical Staff

All physicians who spend 40 per cent or more of their time at the Center have staff positions at the hospital and faculty appointments at Rush Medical College. The proposed ratio of physicians is one physician for every 1,300 patients, and for dentists, one dentist for every 2,500 persons. The ratio of supporting personnel, which includes all persons involved in direct patient care, is one supporting person for every 370 patients.

All full-time physicians are expected to devote full time to the Health Center work, which includes providing additional clinical inpatient services for Health Center patients when hospitalized. Full-time physicians are not expected to have other employment. They spend 80 per cent of their time in the health center and are allotted 20 per cent of their time for hospital work. They are

expected to fulfill their teaching and patient care responsibilities at Presbyterian-St. Luke's Hospital, which does not exceed 10 per cent of their time.

Supporting staff salaries are based on comparability studies in other institutions within the city and are in keeping with the policies of Presbyterian-St. Luke's Hospital.

Full-time physicians are paid on a salary basis commensurate with Presbyterian-St. Luke's Hospital's salary schedule. Part-time physicians' time and salary are calculated on the percentage of a forty-hour week. Physician staffing pattern is shown in Table 1.

TABLE 1
PHYSICIAN STAFFING—1970

Medical Specialty	Number of Physicians	Time Devoted to Center
Medical	2	100%
	2	88%
	2	50%
	5	20%
Mental Health	1	50%
	1	20%
	1	10%
Obstetrics	2	50%
Pediatrics	5	100%
	1	60%
	1	50%
	10	10%
Dentistry	6	100%

Emphasis has been placed on the establishment of new roles for nurses; the public health nurse serves as the family health counselor; clinic nurses have been trained to function in the area of screening, both in pediatrics and in internal medicine; and nurses have received additional training to enable them to provide the majority of well-baby care. A program to train community residents as community health aides was established. The community health nursing teams now consist of one community health nurse and three community health aides. These teams function primarily in the home, with heavy emphasis on health counselling, supportive therapy, resource assistance, clinic attendance evaluation, and morbidity nursing care.

The mental health unit serves in a consultative capacity to all members of the Center staff, both in direct patient care and in in-service training of staff. Members of this unit also serve as consultants to several of the schools in the community as well as to other community agencies. Here again, community residents have been trained as mental health workers, working under the supervision of the social work staff. A unique feature of the mental health unit has been the development of a youth program designed to involve teenagers in a constructive program of art, music, and other cultural activities.

The establishment of the Health Center has had an economic impact on the community, not only as a source of medical care but also as a provider of jobs. Positions for health professionals, laboratory technicians, community health aides, clerical workers, maintenance workers, and many others have been created by the activation of the clinic. In order to bring community residents into these positions, training programs have had to be set up and personnel policies established that allowed for career mobility, both within and outside the clinic.

Patient Utilization

Of the approximately 25,000 residents in the Mile Square target area it is estimated that over 90 per cent of them are eligible to participate in the program. Residents of the community learn about the Health Center primarily through word of mouth, from community residents, from patients who have been served, from public health teams, through block clubs, through meetings, through members of the Mile Square Health Center Advisory Board, and through employees who are residents of the community, as well as through other agencies functioning within the community.

Data on the characteristics of patients, the rate of growth of the registered population, and an analysis of patient visits

and the utilization of services at Mile Square Neighborhood Health Center are shown on Tables 2 to 7.

Table 2 indicates that 97.6 per cent of the registered patients are Black. Males represent 43.5 per cent of the registered patients, females 56.5 per cent. Of all registered patients, 85.1 per cent are 44 years of age or younger.

Tables 3, 4, 5, and 6 give a detailed analysis of patient visits and encounters, by location of visit and by which department or person on the health care team was seen by the patient. For the purpose

TABLE 2
CHARACTERISTICS OF PATIENTS AS OF JUNE 30, 1971

		Index*
Number of patients registered at Mile Square Health Center 7/5/67	3,463	
Number of patients registered at Mile Square Health Center 5/20/68	10,120	100.0
Number of patients registered at Mile Square Health Center 12/31/69	15,724	155.4
Number of patients registered at Mile Square Health Center 12/31/70	18,183	179.7
Number of patients registered at Mile Square Health Center 6/30/71	18,983	187.6

ETHNIC GROUPING	NUMBER	%
White	226	1.2
Black	18,526	97.6
Spanish	47	0.2
Oriental	3	0.0
Unknown	181	1.0

MARITAL STATUS	NUMBER	%
Single	13,551	71.4
Married	2,887	15.2
Widowed	848	4.5
Divorced	385	2.0
Separated	1,312	6.9

SEX DISTRIBUTION	NUMBER	%
Males	8,260	43.5
Females	10,684	56.3
Unknown	39	0.2

AGE DISTRIBUTION	NUMBER	%
Under 1 yr.	445	2.3
1 to 5	3,080	16.2
6 to 11	3,558	18.7
12 to 15	2,257	11.9
16 to 21	2,527	13.3
22 to 44	4,300	22.7
45 to 64	1,765	9.3
65 and up	1,050	5.5
No answer	1	0.0
TOTAL	18,983	

*Difference between time periods shown is a net difference since patients leaving the area or deceased have been removed from these current figures. In actual fact, 24,299 charts have been opened and that number of patients seen since February, 1967.

TABLE 3
MILE SQUARE HEALTH CENTER PATIENT VISIT DATA

	1967	1968	1969	1970
Total Visits (Clinic—Home)	21,412	55,513	87,256	97,886
Clinic Visits (Registered Patients)	17,502	38,833	61,458	67,860
Clinic Visits (Unregistered Patients)	634	812	2,718	5,867
Home Visits (Registered)	2,911	13,325	18,789	19,741
Home Visits (Unregistered)	365	2,543	4,291	4,568
Patients Seen (Registered)	5,949	11,114	12,777	15,215
Patients Seen (Unregistered)	666	2,678	5,633	7,486
PERCENT OF REGISTERED PATIENTS SEEN IN CLINIC:				
Only Once	30.0%	30.8%	22.6%	24.3%
2-4 Times	48.8%	40.6%	36.6%	37.0%
5 or more Times	21.2%	28.6%	40.8%	38.7%

of these tables, an encounter is defined as each face-to-face contact between patient and health care team member. Multiple encounters may occur with each visit. Data on the 11 most frequent diagnoses made by physicians are presented in Table 7.

Hospital Utilization

Tables 8 and 9 show data relative to hospitalization of Mile Square patients at Presbyterian-St. Luke's Hospital. Hospitalization rates were significantly higher during the first year of operation than in any subsequent year. Rates are also well below the national average. Data, however, are limited to information on hospitalization only at Presbyterian-St. Luke's Hospital. More intensive analysis of this experience is being carried out.

Financing

In addition to the grant assistance provided by the OEO which constitutes a major portion of the Center's financing, major efforts have been directed toward obtaining reimbursement from the welfare department under the Title 19 pro-

TABLE 4

ANALYSIS OF PATIENT VISITS TO MILE SQUARE HEALTH CENTER FOR 1968 and 1969

	1968 Reg. & Unreg.		1969 Unregistered		1969 Registered		Totals	
I. TOTAL NO. OF PATIENT VISITS	No.	%	No.	%	No.	%	No.	%
At Clinic	42,409	65.8	2,718	39.2	61,458	71.6	64,176	69.2
At Home	18,908	29.4	4,219	60.8	18,789	21.9	23,008	24.8
Referred to PSLH-HC*	3,105	4.8			5,573	6.5	5,573	6.0
Total Patient Visits	64,422	100.0	6,937	100.0	85,820	100.0	92,757	100.0
II. DISTRIBUTION OF CLINIC VISITS BY INVOLVEMENT OF A DOCTOR								
No. of patient visits to clinic in which a physician was involved	36,860	86.9	581	21.4	48,869	79.5	49,450	77.1
No. of patient visits to clinic in which a physician was not involved	5,549	13.1	2,137	78.6	12,589	20.5	14,726	22.9
Total Patient Visits to Clinic	42,409	100.0	2,718	100.0	61,458	100.0	64,176	100.0
III. DISTRIBUTION OF VISITS BY SPECIALTY SEEN								
Internal Medicine	14,303	38.8	199	34.3	19,742	40.4	19,941	40.3
Pediatrics	17,517	47.5	377	64.9	23,822	48.7	24,199	49.0
Obstetrics-Gynecology	5,040	13.7	5	.8	5,305	10.9	5,310	10.7
Total Patient Visits With Physician Involved	36,860	100.0	581	100.0	48,869	100.0	49,450	100.0
IV. TYPES OF PERSONNEL MAKING HOME VISITS								
Nurses	5,858	31.0	1,318	31.2	5,687	30.3	7,005	30.5
Aides	12,604	66.7	2,852	67.6	12,892	68.6	15,744	68.4
All others	446	2.3	49	1.2	210	1.1	259	1.1
Total No. of Home Visits	18,908	100.0	4,219	100.0	18,789	100.0	23,008	100.0

*Presbyterian-St. Luke's Hospital Health Center

TABLE 5

ANALYSIS OF PATIENT VISITS TO MILE SQUARE HEALTH CENTER FOR 1970

	Unregistered Patients		Registered Patients		Total	
I. TOTAL NO. OF PATIENT VISITS	No.	%	No.	%	No.	%
At Clinic	5,867	56.2	67,860	72.8	73,727	71.1
At Home	4,568	43.8	19,741	21.2	24,309	23.5
Referred to PSLH* Outpatient Specialty Clinics			5,587	6.0	5,587	5.4
Total Patient Visits	10,435	100.0	93,188	100.0	103,623	100.0
II. DISTRIBUTION OF CLINIC VISITS BY INVOLVEMENT OF A DOCTOR						
No. of patient visits to clinic in which a physician was involved	1,508	25.7	56,852	83.8	58,360	79.2
No. of patient visits to clinic in which a physician was not involved	4,359	74.3	11,008	16.2	15,367	20.8
Total Patient Visits to Clinic	5,867	100.0	67,860	100.0	73,727	100.0
III. DISTRIBUTION OF VISITS BY SPECIALTY SEEN						
Internal Medicine	460	30.5	23,760	41.8	24,220	41.5
Pediatrics	1,025	68.0	26,562	46.7	27,587	47.3
Obstetrics-Gynecology	23	1.5	6,530	11.5	6,553	11.2
Total Patient Visits with Physician Involved	1,508	100.0	56,852	100.0	58,360	100.0
IV. TYPES OF PERSONNEL MAKING HOME VISITS						
Nurses	1,573	34.4	5,756	29.2	7,329	30.1
Aides	2,970	65.0	13,835	70.1	16,805	69.1
All others	25	0.5	150	0.7	175	0.7
Total No. of Home Visits	4,568	100.0	19,741	100.0	24,309	100.0

*Presbyterian-St. Luke's Hospital

TABLE 6
UTILIZATION OF HEALTH CENTER: OUTPATIENT ENCOUNTERS* (quarterly basis)

Patient seen by:	1970				
	Jan-Mar	Apr-June	July-Sept	Oct-Dec	Total
PHYSICIANS					
Internists	5,999	6,055	6,069	6,097	24,220
Pediatricians	7,905	6,750	6,606	6,328	27,589
Obstetricians	1,479	1,751	1,707	1,616	6,553
TOTAL	15,383	14,556	14,382	14,041	58,362
CLINIC NURSING TEAM					
TOTAL**	21,172	19,593	19,413	18,187	78,365
Team only	5,789	5,037	5,031	4,146	20,003
% of Total	27.3	25.7	25.9	22.7	2.5.5
COMMUNITY NURSING TEAM					
P.H. Nurse	1,241	1,694	1,960	2,434	7,329
Community Aides	3,565	3,827	4,262	5,151	16,805
TOTAL	4,806	5,521	6,222	7,585	24,134
% of total Aides	74.1	69.3	68.4	67.9	69.6
Mental Health Team	2,076	1,425	534	315	4,350
Not reported	76	166	30	44	316
Others	460	673	520	648	2,301
Total Encounters	43,973	41,934	41,101	40,820	167,828
Daily Average***	666.3	635.4	622.7	618.5	

* Definition of encounter: each face-to-face contact; multiple encounters may occur with each visit.
** Includes support services to physicians.
*** 22 days/month—66 days/quarter.

gram. Arrangements have been made for the satisfactory reimbursement to the program for medical care provided to the certified beneficiaries of the welfare and public aid program. Similar arrangements have been made with Illinois Blue Cross-Blue Shield for the reimbursement of patients receiving medical care under the Title 18 program.

Approximately 40 per cent of the eligible participants are potentially eligible for ambulatory care services under Title 18 and 19 programs. Among the hospitalized patients, approximately 80 per cent are eligible for reimbursement. Some monies are received on a prorated basis for services rendered to patients who have the ability to pay for at least part of their medical expenses.

Capital construction of the new Health Center is being carried out under Title XI of the Group Practices Act.

TABLE 7

ELEVEN MOST FREQUENT PRIMARY DIAGNOSES MADE BY PHYSICIANS

(Excluding Pregnancy) for 1970

1970

DIAGNOSIS	NUMBER	% OF TOTAL RECORDED DIAGNOSES
1. Upper Respiratory Infections	5,217	18.1
2. Hypertensive Diseases	2,928	10.1
3. Diabetes Mellitus	1,851	6.4
4. Obesity	1,347	4.6
5. Asthma	1,094	3.8
6. Lacerations and Open Wounds	1,044	3.6
7. Symptoms, Senility, and Ill-Defined Conditions	842	2.9
8. Otitis Media	745	2.5
9. Pharyngitis	740	2.5
10. Bronchitis	575	1.9
11. Tonsillitis	470	1.6
TOTAL ABOVE	16,853	58.5
ESSENTIALLY HEALTHY	8,349	29.1
OTHERS	3,570	12.4
TOTAL PRIMARY DIAGNOSES RECORDED	28,772	

TABLE 8

MILE SQUARE HEALTH CENTER

HOSPITALIZATION EXPERIENCE 1967, 1968, 1969, 1970

MILE SQUARE Health Center	1967	1968	1969	1970
Total population registered	7,465	12,230	15,724	18,183
Total patients hospitalized (excluding Obstetrics)	945 (489)	1,295 (743)	1,279 (838)	1,611 (1,047)
Total days of hospitalization (excluding Obstetrics)	6,998 (5,319)	9,920 (7,903)	11,545 (9,927)	14,829 (12,405)

MEASURES OF INPATIENT CARE	Feb-Dec 1967	Jan-Dec 1968	Jan-Dec 1969	Jan-Dec 1970
1. Obstetrical Service Included				
A. Annual discharges per 1,000 registered population	126.5	105.9	81.2	88.5
B. Average length of stay (days)	7.4	7.7	9.0	9.2
C. Annual patient day rate per 1,000 registered population	937	811	734	816
2. Obstetrical Service Excluded				
A. Annual discharges per 1,000 registered population	65.5	60.8	53.2	57.5
B. Average length of stay (days)	10.9	10.6	11.8	11.8
C. Number of hospital days per 1,000 registered persons per year	712	646	627	682

TABLE 9
MILE SQUARE HEALTH CENTER
HOSPITALIZATION EXPERIENCE
1970

SERVICE	No. of Discharges	Per cent of all Discharges	No. of Days	Average Length of Stay
Medicine	379	23.5	6,423	16.9
Surgery	248	15.4	2,891	11.7
Obstetrics	564	35.0	2,424	4.3
Pediatrics*	392	24.3	2,325	5.9
Psychiatry	28	1.7	766	27.4
TOTAL	1,611	100.0	14,829	9.2
		1969		
Medicine	248	19.4	4,339	17.5
Surgery	236	18.5	2,357	10.0
Obstetrics	457	35.7	1,684	3.7
Pediatrics*	323	25.3	2,930	9.1
Psychiatry	15	1.2	235	15.7
TOTAL	1,279	100.1	11,545	9.0
		1968		
Medicine	208	16.1	3,288	15.8
Surgery	194	15.0	1,996	10.3
Obstetrics	552	42.6	2,017	3.7
Pediatrics*	334	25.8	2,569	7.7
Psychiatry	7	.4	50	7.1
TOTAL	1,295	99.9	9,920	7.7

*Includes Pediatrics, Medicine and Surgery

Conclusion

This brief summary has outlined the origin and development of an extensive and innovative program of health care delivery for the urban poor. The interacting problems promise change and further development of great interest and significance.

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4. Lepper MH, Lashof JC, Lerner M, German J, Andelman SL: Approaches to meeting health needs of large poverty populations. Amer J Public Health **57**:1153-1157, July, 1967

ABSTRACTS

OF PUBLICATIONS BY THE STAFF

BIOCHEMISTRY

Booyse FM, Rafelson ME Jr: Human platelet contractile proteins: Location, properties and function. *Ser Haemat IV:152-174, 1971*

The development of an immunohistochemical technique for studying the ultrastructural localization of cellular antigens has enabled us to establish the presence of human platelet contractile proteins on the external surface of the cell as well as in the platelet cytoplasm. Comparison of the incorporated radioactivity and physicochemical properties of the intact contractile proteins and myosin fractions obtained from these two locations indicated that the surface-localized contractile protein (S-thrombosthenin) and the cytoplasmic contractile protein (C-thrombosthenin) of the platelet were distinctly different. Specific antibody staining was used as a means of studying the conformational changes induced in S-thrombosthenin of intact platelets after treatment with thrombin and ADP. S-thrombosthenin changes induced by thrombin proceed in the following sequence:

(1) Short exposure to thrombin resulted in reversible unfolding (dissociation) and projection of surface extended structures, immunohistochemically identifiable as S-thrombosthenin (or its subunits); these extended surface structures were very similar if not identical to purified S-thrombosthenin treated with the antibody staining technique.

(2) Longer exposure to thrombin resulted in the extensive formation of distinct interplatelet bridges, also immunohistochemically identifiable as S-thrombosthenin; these bridges appeared to form over a maximum interplatelet distance of about 1500-2000 A.

(3) Extremely rapid shortening (contraction) and thickening of the interplatelet S-thrombosthenin bridges, resulting in a complete blending of the external platelet coats.

From these data we have concluded that the surface-localized contractile protein of human platelets, S-thrombosthenin, is directly involved in the molecular mechanism of platelet aggregation. Experimental evidence presented here provides strong support for the contractile protein model for platelet aggregation proposed previously. The proposed model involves the formation of intermolecular S-thrombosthenin bridges between adjacent cells, which in turn can contract, drawing the platelets into a tight mass or thrombus.

Harrison WH, Gray RM: Catecholamine stimulation of brain hexokinase. *Biochim Biophys Acta 237:391-394, 1971*

Catecholamines stimulate brain hexokinase when Mg^{2+} and H^{+} concentration levels are suboptimal and the concentration of the phosphate acceptor (glucose or 2-deoxyglucose) exceeds the half-saturation level. The catechol group is required and the sidechain substituent alters the activity. Other types of phosphate-transferring enzymes are not stimulated; yeast hexokinase is stimulated but the reaction characteristics differ. The results suggest a physiologic control mechanism for hexokinase in which tissue levels of Mg^{2+}, H^{+} and glucose serve as metabolic signals.

von Friedel R, Mattenheimer H: Release of enzymes from thrombocytes during blood clotting of mouse and guinea pig. *Z Clin Chem u Klin Biochem 9:103-106, March, 1971*

The effect of blood clotting on the activities in serum of lactate dehydrogenase (EC 1.1.1.27), malate dehydrogenase (EC 1.1.1.37), aspartate aminotransferase (EC 2.6.1.1), alanine aminotransferase (EC 2.6.1.2) and γ-glutamyl transpeptidase (EC 2.3.2.1) was studied in the mouse and in the guinea pig. In both species enzymes are released from thrombocytes into the serum during clotting. The extent of the enzyme liberation is such that activity measurements in serum are of restricted or no diagnostic value, if high activities of the respective enzymes are also present in the thrombocytes (e.g., lactate and malate dehydrogenase). It appears that enzymes with lower molecular weights are released at a slightly faster rate than those with higher molecular weights. γ-Glutamyl transpeptidase is set free from guinea pig thrombocytes despite its firm binding to cell structures. The enzyme is either solubilized during the clotting process, or subcellular particles are liberated to which the enzyme is attached.

COMMUNITY HEALTH

Ostfeld AM, Shekelle RB, Tufo HM, Wieland AM, Kilbridge JA, Drori J, Klawans H: Cardiovascular and cerebrovascular disease in an elderly poor urban population. *Amer J Public Health 61:19-29, 1971*

As part of a cohort study of the epidemiology of cerebrovascular attacks in an elderly urban poor population, this paper describes the samples in the cohort and how they were studied, data on prevalence of cardiovascular and cerebrovascular diseases, and the adequacy of management of such disorders in this group.

DERMATOLOGY

Malkinson FD, Griem ML, Marianovic R: Persistent impairment of hair growth after single large doses of x-rays. *Radiat Res 43: 83-91, July 1970*

Telogen mouse hairs treated with single doses of 2000 to 2500 rads showed persistent impairment of postirradiation growth as measured by determinations of overall hair length. Reductions in length of surviving hairs, compared to contralateral controls, averaged 27 per cent for the hairs newly grown postirradiation. Subsequent hair generations showed no significant recovery: reductions in length of hairs from the same treatment sites averaged 33 per cent ten months after irradiation. Cyclic regrowth of hair in these areas was also unusually slow: after plucking, hair density was not fully restored in irradiated areas for four weeks or longer, in contrast to the normal replacement time of two-and-one-half weeks observed in plucked control sites. This change was demonstrable up to 14 months postirradiation. Exposure of telogen hairs to a somewhat smaller dose of 1500 rads resulted in a 12 per cent reduction of length in the generation of hairs growing immediately postirradiation, followed by complete recovery in the subsequent cycle of hair growth.

The persistence of effects in the animals subjected to high doses of radiation may be the result of overall reduction in stem cell pool size since investigations with tritiated thymidine showed that cell generation cycles were almost identical in treatment and control sites but that the mitotic index was substantially reduced in the irradiated areas.

GASTROENTEROLOGY

Hardison WG: Metabolism of sodium dehydrocholate by the rat liver: Its effect on micelle formation in bile. *J Lab Clin Med 77:811-820, May, 1971*

Dehydrocholate is a potent choleretic, presumably because its osmotic activity in bile is not diminished by micelle formation. Evidence for this assumption is indirect. The extent to which dehydrocholate may be metabolized to micelle-forming bile salts by the liver has never been investigated. By a combination of thin-layer and gas-liquid chromatography, six separate bile salt peaks derived from dehydrocholate can be identified in bile from rats infused with dehydrocholate. One of these peaks migrates as cholic acid on thin-layer chromatography. Its derivatives have retention times identical to those of cholic acid derivatives on several gas-liquid chromatographic column systems. Moreover, bile from animals injected with dehydrocholate carboxy-^{14}C contained carboxy-^{14}C cholic acid. Although cholic acid, as its taurine conjugate, can form micelles, it is a minor metabolite of dehydrocholate. The micelle-forming capacity of dehydrocholate metabolites was tested *in vitro*. Bile salts were extracted from bile of rats infused with dehydrocholate and tested for their ability together with lecithin to solubilize cholesterol in aqueous solution. Their ability to solubilize cholesterol was 10 to 17 per cent that of equimolar solutions of sodium taurocholate. A large part of this micelle-forming capacity may be attributed to the cholic acid formed from dehydrocholate. The data indicate that metabolites of dehydrocholate, with the exception of cholic acid, have little micelle-forming capacity.

HEMATOLOGY

Bachmann F: The paradoxes of disseminated intravascular coagulation. *Hosp Prac 113-126, Sept 1971*

One is the occurrence of hemorrhage as the end result of excessive clotting; another, the effectiveness of an anticoagulant in helping to curb the bleeding. A wide variety of disease states may produce the hypercoagulability that triggers the chain reaction leading to disseminated intravascular coagulation. These include conditions that release procoagulants into the blood, slow blood flow, injure the vascular endothelium, or compromise the integrity of the liver and the reticuloendothelial system.

MICROBIOLOGY

Wolfe LG, Griesemer RA: Feline infectious peritonitis: Review of gross and histopathologic lesions. *J A V M A 158:987-993, March, 1971*

The macroscopic lesions in cats with naturally occurring feline infectious peritonitis are characterized by excessive abdominal fluid and diffuse fibrinous peritonitis. Histopathologically, characteristic lesions include a layer of fibrinous exudate distributed on the peritoneal serosal surfaces, subserosal and subcapsular inflammation and necrosis, and periorchitis. Focal hepatic necrosis, pleuritis, and meningitis are present in 20 to 40 per cent of the affected cats. Lesions in the experimental disease are usually less severe, but qualitatively identical to those which characterize the spontaneous infections. Thus far, the pathogenesis of the disease is poorly understood.

Mohr JR, Mattenheimer H, Holmes AW, Deinhardt F, Schmidt FW: Enzymology of experimental liver disease in marmoset monkeys. II. Experimental hepatitis. *Enzyme 12:161-179, 1971*

Marmosets have been shown to develop hepatitis after inoculation of serum from patients with viral hepatitis. The activity alterations of lactate dehydrogenase, isocitrate dehydrogenase, alanine aminotransferase, aspartate aminotransferase, glutamate dehydrogenase, glucose-6-phosphate dehydrogenase, and phosphogluconate dehydrogenase in serum and liver tissue of marmosets with hepatitis suggest that these animals suffer from a mild but relatively protracted hepatocellular injury. Although the enzyme patterns are not identical to those seen in human viral hepatitis, they appear to resemble more closely the picture seen in that disease than in any other.

Mohr JR, Mattenheimer H, Holmes AW, Deinhardt F, Schmidt FW: Enzymology of experimental liver disease in marmoset monkeys. I. Patterns of enzyme activity in liver, other organs and serum of marmosets, compared to man and other mammals. *Enzyme 12:99-116, 1971*

The activities of lactate dehydrogenase, isocitrate dehydrogenase, malate dehydrogenase, alanine aminotransférase, aspartate aminotransferase, glutamate dehydrogenase, glucose-6-phosphate dehydrogenase, phosphogluconate dehydrogenase and creatine phosphokinase were determined in extracts from liver (cytoplasmic and mitochondrial compartments), other organs and in serum of healthy, wild-caught, laboratory-acclimatized marmosets (Saguinus species). The data were to serve as baseline and control values for the study of experimental liver diseases. Striking species differences were found when the activity levels and enzyme patterns of liver and serum were compared to data of man, horse, dog, guinea pig, rat and mouse.

Falk LA, Wolfe LG, Deinhardt F: Oncogenesis of *herpesvirus saimiri* in marmosets. *Fed Proc 30:2, March-April, 1971*

Herpesvirus saimiri (HVS), latent in squirrel monkeys, induces malignant lymphomas in cotton-top (CT) and white-lipped (WL) marmosets. CT are consistently susceptible to HVS and in preliminary experiments, never survived longer than 35 days PI. For these reasons, CT were selected for a pathogenesis study: animals were sacrificed at three or four day intervals, 3 to 33 days PI. Focal necrosis of parenchymal cells was evident in several organs three to seven days PI, suggesting the early viral effect was cytocidal. A generalized proliferative response composed of reticulum cells or lymphoblasts began 7 to 10 days PI and progressed to massive replacement of the normal cytoarchitecture of many organs. Compared to CT, the disease in WL was characterized by a more protracted clinical course, pronounced leukocytosis and lymphocytosis, and less organ replacement by primitive cells. Inclusion bodies or viral particles were not seen in the early cytocidal lesions or in the neoplastic cells by light or electron microscopy. HVS was isolated from lymphoid organs early in the disease, but in later stages, was isolated from tissues of all organ systems. HVS and antibodies to HVS were first detected 14 days PI in whole blood and serum respectively. Viral antigens were not demonstrated in any tissues by immunofluorescence.

McDonald R, Wolfe L, Deinhardt F: *In vitro* assay for ST-feline fibrosarcoma virus. *Fed Proc 30, Mar-Apr 1971*

Two C-type RNA viruses isolated from naturally occurring feline fibrosarcomas, Snyder-Theilen (ST-FXV) and Gardner (G-FSV) isolates, consistently induce sarcomas in marmoset monkeys and transform marmoset cells *in vitro*. Marmoset tumor cells cultured *in vitro* produce C-type virus; ST-FSV produced by one marmoset tumor cell line was used in this study.

ST-FSV-induced foci in cultures of feline embryonic fibroblasts (FEF) and newborn marmoset fibroblasts (MF). The indicator cells in plastic flasks were exposed, when approximately 60 per cent confluent, to cell-free extracts of cultured tumor cells. An agar overlay (Bacto-agar) was applied 12 to 72 hours later. Foci of loosely arranged, round cells were evident eight to ten days after infection. By 21 days the foci in FEF were morphologically unchanged whereas the foci in MF had two morphologic patterns: tightly packed round cells or a loose meshwork of fusiform and round cells. The morphologic growth patterns of cell clones derived from the two types of foci are now under study. The focus assay in FEF yielded higher titers of ST-FSV than parallel assays in MF. The titration patterns, i.e., ratio of focus counts vs. virus dilutions of ST-FSV, indicate that the FSV used in these studies was either competent or the preparations contained an excess of "helper" virus.

Junge U, Hoekstra J, Deinhardt F: Stimulation of peripheral lymphocytes by allogeneic and autochthonous mononucleosis lymphocyte cell lines. *J Immun 106:1306-1315, May, 1971*

Cultures of peripheral lymphocytes obtained during the acute phase of infectious mononucleosis (IM) were established. Mitomycin C-inhibited cells of these cultures caused abnormally high transformation rates in mixed cultures (MLR) with allogeneic peripheral lymphocytes and to a lesser degree they also stimulated antochthonous peripheral lymphocytes obtained from the same persons three to nine months after their acute disease. This stimulation seems not to be caused by Epstein-Barr virus (EBV), present in the IM cultures, because concentrated EBV preparations did not stimulate the convalescent lymphocytes, and allogeneic lymphocytes from infants with and without circulating EBV antibodies responded equally well in the MLR with cultured IM lymphocytes, stored in liquid nitrogen or cultured, were demonstrated in convalescent IM sera by the indirect membrane fluorescence technique. Blastogenic activity for both allogeneic and autochthonous lymphocytes was found in the cell-free supernatants of these IM lymphocyte cultures and was probably associated with cell membrane fragments.

Jensik SC, Northrop RL: Incorporation of radioactive seleno-(^{75}Se)-methionine into mumps virus. *Appl Microbiol 21:451-455, 1971*

Mumps virus was grown in embryonated chicken eggs in the presence of radioactive seleno-(^{75}Se)-methionine. Virus in the allantoic and amniotic fluids was concentrated in a sucrose density gradient, and a peak of viral material coincided with a significant peak of ^{75}Se-radioactivity. The radioactivity was acid-insoluble and remained associated with the virus after purification by erythrocyte adsorption and elution and centrifugation on a second sucrose density gradient. After amino-acid hydrolysis of the radioactive virus, only ^{75}Se-methionine was recovered by chromatographic analysis. These results demonstrate that the radioactive ^{75}Se-methionine was incorporated into protein of infectious mumps virus.

NEUROLOGY

Klawans HL Jr, Paulson GW: Primitive reflexes in parkinsonism. *Confin Neurol 33: 25-32, 1971*

Several of the primitive reflexes, such as corneomandibular, palmomental, and the glabella tap sign are common in parkinsonism. The glabella tap sign is particularly characteristic, and may change during the course of the therapy with L-dopa. The glabellar reflex is less likely to reverse under L-dopa when other primitive reflexes are associated with it.

Patel KK, Hartmann JF, Cohen MM: Ultrastructural estimation of relative volume of extracellular space in brain slices. *J Neurol Sci 12:275-288, 1971*

Ultrastructural estimation of the relative volume of the interstitial space in guinea pig cerebral cortex slices incubated under various experimental conditions has been made.

The interstitial space volume was 3 per cent in a slice incubated aerobically for 10 minutes in a medium enriched with 10 m*M* glucose as well as in an unincubated slice suspended in a medium lacking glucose. Under the optimal condition of 20-minute aerobic incubation in a medium containing 10 m*M* glucose, the interstitial space volume was 7.5 per cent. It was also 7.5 per cent after 20-minute anaerobiosis. However, the volume of intracellular compartment was much larger in the anaerobically-incubated slices. With longer aerobic incubation, the interstitial space volume was increased, reaching 13 per cent at one hour. The alterations in the size of the interstitial space caused by deprivation of glucose, or both glucose and oxygen were studied. The interstitial space volume was also determined in slices incubated in the presence of L-glutamic acid as substrate or in the combined presence of glucose and L-glutamic acid.

Measurements were made of the astrocytic cytoplasm volume in electron micrographs prepared from slices incubated under optimal conditions. It is suggested that the extracellular space estimated by biochemical methods includes both the true interstitial space and the fluid compartment represented by astrocytic cytoplasm. This inclusion of astrocytic cytoplasm into a functional extracellular space is consistent with previously-reported ultrastructural evidence for a high sodium content of cortical astrocytes.

Cheifetz DI, Garron DC, Leavitt F, Klawans HL, Garvin JS: Emotional disturbance accompanying the treatment of parkinsonism with L-dopa. *Clin Pharmacol Ther 12: 56-61, Jan-Feb 1971*

This paper reports a study, using systematic observation, interview, and psychological examination, in a sample of 34 patients receiving L-dopa for parkinsonism. Our results do not support the suggestion that disturbances of mood and behavior are to be expected. We concluded that the chances of adverse emotional side reactions to L-dopa appear to be minimal when the dosage level does not exceed 4 Gm per day and the subjects are emotionally stable prior to treatment.

Klawans HL Jr, Zeitlin E: L-dopa in parkinsonism associated with cerebellar dysfunction (probable olivopontocerebellar degeneration). *J Neurol Neurosurg Psychiat 34: 14-19, 1971*

Two patients with combined cerebellar and Parkinsonian features consistent with olivopontocerebellar degeneration were treated with long-term oral L-dopa. Both patients showed improvement of the Parkinsonian symptoms but the cerebellar symptoms were unchanged. It is suggested that the Parkinsonian manifestations of this syndrome are related to loss of dopamine in the striatum secondary to lesions of the *substantia nigra*. It is suggested that other patients with similar disorders should be given a trial with L-dopa.

OBSTETRICS

Sutton DMC, Hauser R, Kulapongs P, Bachmann, F: Intravascular coagulation in *abruptio placentae*. *Amer J Obstet Gynec 109:604-14, 1971*

Sequential coagulation profiles were performed in a series of 17 consecutive patients with *abruptio placentae*. These patients were divided into three groups on the basis of the fibrinogen

concentration and the severity of coagulation defects. Group A consisted of seven patients with no obvious coagulation disturbance and fibrinogen concentrations comparable to those found in normal women at term. Statistical analysis, however, revealed a significantly decreased mean level of factor VIII and a prolonged Clauss fibrinogen time. Group B consisted of five patients with fibrinogen concentrations between 200 and 300 mg per cent and clearly disturbed coagulation profiles characterized by decreased levels of factors V, VIII and XIII and by the presence of circulating fibrin-split products. Group G consisted of the five most severely affected patients. The concentrations of fibrinogen and factor V were lower than those in Group B. In addition, these patients differed from Group B in that the vitamin K-dependent factors II and X were decreased. Clinical severity and extent of bleeding increased from Group A through Group C. Tests for increased systemic fibrinolysis were, in general, negative. This result and the occurrence of severe deficiencies of fibrinogen and other clotting factors, which cannot be explained on the basis of blood loss alone, indicate that the coagulation disturbance was caused by consumption coagulopathy. Evacuation of the uterus resulted in prompt improvement in all patients.

Cavanagh D, Rao PS, Sutton DMC, Bhagat BD, Bachmann F: Pathophysiology of endotoxin shock in the primate. *Amer J Obstet Gynec 108:705-722, Nov. 1970*

The intravenous administration of coliform endotoxin to healthy baboons produced a precipitous fall in renal artery flow, a profound drop in the platelet count, and a marked increase in plasma norepinephrine levels within three minutes. There was no significant change in aortic pressure, central venous pressure, cardiac output, or circulation time over this period. After three to ten minutes, simultaneous shortening of the plastic clotting time and intensive stimulation of the fibrinolytic system occurred. By 60 minutes, progressive deterioration of the coagulation mechanism had occurred. After the initial rise, the plasma norepinephrine levels began to fall and were near normal at 120 minutes. Response of isolated atria from baboons pretreated with endotoxin showed that endotoxin pretreatment caused reduced responsiveness to l-norepinephrine and tyramine. These studies have clarified the pathophysiology of endotoxin shock in the primate to some degree, suggesting that selective vasospasm, intravascular coagulation, and reduced myocardial response all play a part.

PATHOLOGY

Henson D, Neapolitan C: Pathogenesis of chronic mouse cytomegalovirus infection in submaxillary glands of C_3H mice. *Amer J Path 58:255, 1970.*

The murine cytomegalovirus (MCMV) causes a chronic infection in the submaxillary glands of the C_3H/Anf and ICR/HA mice. After IP infection, virus titers reach peak levels in the submaxillary glands within 3 weeks. After this, virus titers decrease more rapidly in C_3H than in ICR mice. Decreasing titers are associated with interstitial inflammation in the submaxillary glands, acinarrhexis, and degeneration of infected cells. Inclusions and infectious virus persist longer in ICR mice. Special strains showed that as long as the reticulum network around the acini remained intact, the acini remained intact, and infected cells did not degenerate. Penetration of acini by inflammatory cells was accompanied by fragmentation of the reticulum network, acinarrhexis, and degeneration of infected cells.

Administration of cortisone during chronic infection abolished the inflammatory reaction in the submaxillary glands. Virus titers did not decrease, but remained elevated at peak levels. Despite chronic cortisone administration, disseminated infection did not occur. Cortisone-treated, chronically infected mice were resistant to reinfection with lethal doses of MCMV.

The conclusions are made, chiefly from histologic observations, that chronic MCMV infection in the submaxillary glands depends on persistence of intact inclusion-bearing cells

and that chronic inflammatory cells eventually terminate chronic infection.

It is proposed that the argyrophilic reticulum network in the submaxillary glands protects infected cells with acini from interstitial inflammatory cells and that this is one mechanism of chronic cytomegalovirus infection in glandular organs.

Eisenstein R, Arsenis C, Kuettner KE: Electron microscopic studies of cartilage matrix using lysozyme as a vital stain. *J Cell Biol 46:626-631, 1970.*

Egg white LYS forms complexes with at least some cartilage polysaccharides which are visible by electron microscopy. These complexes are heterogeneously distributed in the tissue in patterns fitting some of the available chemical data, thus suggesting that LYS may be a useful histochemical tool for the study of cartilage ultrastructure.

RADIOLOGY

Alcorn FS, O'Donnell E, Ackerman LV: The protocol and results of training non-radiologists to scan mammograms. *Radiology 99:523-529, June 1971*

The authors have trained and tested registered radiological technologists to determine whether they can function as scanners in a simulated screening situation. "Logic flow sheets" or "decision trees" were used as the principal teaching device. It was found that the scanners were able to perform creditably when compared to an expert radiologist tested by the same examination; however, in many instances true-positive rates were attained at the sacrifice of a good true-negative rate. The accuracy of the scanners is reported, as well as sources of error and a discussion of error correction.

RUSH-PRESBYTERIAN-ST. LUKE'S

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DISSOLUTION OF GALLSTONES

William G. M. Hardison

In a previous issue of the Bulletin, I made two indictments: I called the gallbladder an organ which did more harm than good, and I suggested that researchers in the field of biliary physiology had contributed little towards the solution of a number of serious clinical problems, most notably cholelithiasis.[1] In the past year the situation has changed: the gallbladder still does more harm than good, but the fruits of basic physiological research are beginning to ripen. Recently a group of authors reported dissolution of gallstones in patients by long-term feeding of the bile salt, chenodeoxycholic acid.[2] This clinical trial was a direct application of basic physiological, biochemical and biophysical principles laboriously formulated over the years by a large number of investigators in various laboratories. As an example of application of basic research to solution of clinical problems, the sequence of events leading to this clinical trial are worth recounting.

I shrink from the task of tracking down the first reported case of cholelithiasis in man—to do so, I suspect, would require intimate knowledge of hieroglyphics. The fact that most gallstones in man are composed predominantly of cholesterol is a recent discovery (perhaps in the early-to-mid 1800's). At that time the problematic question was not, "Why do gallstones occur?" but rather "Why do not gallstones always occur?" Chemists realized cholesterol was insoluble in simple aqueous solution, and the job of physicians was to discover why bile could carry cholesterol in solution at all. In the first half of the 20th century, speculation abounded concerning this subject. Most investigators agreed that bile salts were in part responsible for solubility of cholesterol in bile. They also realized that other substances were necessary since bile did not contain enough bile salt to solubilize the amount of cholesterol actually in solution. Until 1954 the most popular theory was that biliary fatty acid, together with bile salts, solubilized cholesterol. Isaksson[3] in 1954, however, laid this theory to rest by demonstrating that lecithin was the substance which, together with bile salts, permitted solubilization of cholesterol. At last, it seemed, researchers had a firm handle with which to grip the problem of cholelithiasis: they could simply measure biliary bile salt, lecithin, and cholesterol. This information should allow them not only to identify persons prone to cholelithiasis but also to identify the deficiencies in the bile which led to cholelithiasis.

Not true, however. It was unknown, for instance, how much weight to assign to each of the three substances: cholesterol (C), lecithin (L), and bile salt (B),

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in assessing "goodness" or "badness" of bile. Ratios (C/L, C/B, C/B+L, etc.) were devised to try to separate "lithogenic" from normal bile, but with generally poor and variable success. Physicians, reasoning that bile salt and phospholipid promoted biliary cholesterol solubility, tried to dissolve stones or tried to achieve more favorable ratios by feeding these substances. Again, they had little success. Although their reasoning was logical, their lack of knowledge barred success. They had no firm understanding of the physicochemical interaction of bile salt, cholesterol and lecithin. They failed to realize that biliary excretion rates of each of these substances were interdependent and certainly not a simple function of ingestion.

During the mid-sixties, our knowledge of the physicochemical interactions of bile salt, lecithin, and cholesterol was greatly augmented by the work of Dr. D. M. Small and associates working in France with Dr. Derivichian. Dr. Small described in detail the phase changes which occur during alterations in the composition of the quarternary system: bile salt, cholesterol, lecithin, and water.[4] Application of these data to human cholelithiasis allowed Admirand and Small clearly to separate, on the basis of biliary composition, patients with cholelithiasis from normals. In so doing, they provided researchers in the field a firm standard by which to measure lithogenic potential of bile. The triangular phase diagram is now a familiar sight to all involved in research on cholelithiasis and biliary lipid excretion. Although not uniformly accepted as impeccable, it is the only method which allows consideration of all three biliary components in assessing whether a bile sample is more or less nearly saturated with cholesterol.

Also, in the 1960's, Dr. A. F. Hofmann began a series of studies in Sweden which were to help investigators approach the problem of cholelithiasis. These studies encompassed not only the basic chemistry and physical chemistry of bile salts, but also their metabolism in man. Long before bile salts had become "popular" in our country, Swedish investigators had delineated the major pathways of bile salt synthesis, metabolism, and excretion, in animals and man. Dr. Hofmann extended this knowledge and applied it to the process of fat absorption in man. The importance of micelle formation in solubilizing the products of intestinal lipolysis became well known.[6] The critical importance of ileal bile salt absorption in maintaining the body's bile salt pool was realized, and the effect of bile salt depletion upon fat absorption was defined.[7] The role of the liver in maintaining the bile salt pool became common medical knowledge.[8] At the Mayo Clinic, Dr. Hofmann has continued to apply basic knowledge which he and others have derived to problems of human disease. The most important contributions with respect to cholelithiasis, however, were probably those dealing with bile salt metabolism.

Of course the foregoing is an oversimplification. An enormous number of investigators contributed basic knowledge which has brought us to our present degree of sophistication *vis-a-vis* cholelithiasis. By 1970, then, investigators were in a stronger position to tackle again the problem of cholelithiasis. In 1971, Vlahcevic and associates,[9] by using radioactive tracer techniques, found that patients with cholelithiasis had smaller total bile salt pools than normal. Other investigators had noted that depletion of the bile salt pool by interruption of the bile salt enterohepatic circulation resulted in bile more nearly supersaturated with cholesterol than bile collected before interruption.[10] The reasonable thought occurred: if patients with cholelithiasis have small bile salt pools, and if a small bile salt pool yields more nearly supersaturated bile, then feeding bile salt should enlarge the pool in patients with cholelithiasis and desaturate their bile. Subjects were once again fed bile salt—this time purified, not crude bile extract. Degree of bile saturation with cholesterol was assessed by Small's phase diagram. Sodium taurocholate (conju-

gated trihydroxy bile salt) did not desaturate bile, but the dyhydroxy bile salt, chenodeoxycholate, did. Without further ado, patients with gallstones were fed chenodeoxycholate to see if gallstones would dissolve. The patients got diarrhea from the bile salt, but after a number of months of feeding, gallstones dissolved or grew smaller in three of five patients.[2] Such therapy has several obvious drawbacks (cost of drug, long-term administration, production of diarrhea) and a few less obvious drawbacks.[11] Nonetheless, this therapy derived from basic, at one time seemingly irrelevant, knowledge probably does work.

Use of chenodeoxycholate to dissolve gallstones, however, is not quite the triumph of experimental rationality that it might seem—it is still essentially empirical. We do not know why it works and cannot know why it works until we have more knowledge of the mechanisms of biliary lipid excretion. Current knowledge of biliary lipid excretion allows us to explain why taurocholate does not work. I mentioned previously that bile salt, lecithin, and cholesterol excretions were interdependent. It has been shown that the excretion of biliary lipid is dependent upon the excretion of bile salts over a considerable range.[12,13] The ability of bile salt to promote biliary lipid excretion is probably the result of its ability to form mixed micelles with lecithin and cholesterol and hence to solubilize them into bile.[12] This explains the old and new observation that feeding bile salt may increase biliary bile salt excretion, but also increases biliary cholesterol excretion so that no net gain in solubility of cholesterol occurs.[12] This relationship does not hold over the entire range of biliary salt excretion rates; it fails at very low bile salt excretion rates (depleted bile salt pool).[12] At such rates proportionately more cholesterol seems to be excreted than at high rates and bile may become supersaturated. Why does this occur? Whatever the mechanism, it may hold an important clue as to why some people get gallstones. Does chenodeoxycholate alter or suppress this mechanism? Does it selectively promote lecithin excretion over cholesterol excretion and thereby produce a less saturated bile? If so, it is critical to determine how and why this occurs and how and why taurocholate cannot produce this effect. Dissolution of gallstones with chenodeoxycholic acid, I am sure, will produce more perplexing "whys?" for investigators than patient-cures for doctors in the immediate future.

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THE NATURAL HISTORY OF DISEASE: BIOLOGICAL VARIABILITY IN MAN

Frederick Sargent II

INTRODUCTION

My contribution to these lectures on the natural history of disease will focus on human biological variability. Two threads will comprise my skein, but these threads are concepts, clues that only suggest the shape of the final skein. You will have to take the next steps that will ultimately bring these threads together. The skein that I visualize unites organism and environment in an understanding of the probable health experiences of an individual. The basic question that you must ask to achieve this understanding is, What are the organismic and environmental antecedents of disease?

We deal with a medical problem that is as old as the art itself. Hippocrates wrote of it more than two millennia ago. In the interim we have added some details, but we are far from the final synthesis. Ryle[1] pointed out that disease was Nature's health-experiment with man. He observed, however, that "Laboratory physiology can only tell us a tithe of the health-experiment. We have need of a broader and more observational human physiology, more cognizant of human variety. Every man is endowed at birth by his parents and ancestors with a type of constitution built of anatomical, physiological, immunological, and psychological material which will help determine his course through life and his reactions to environmental stress or injury. With the aid of family histories and observations of physical and mental types we may learn to recognize or predict certain liabilities in the way of disease . . . But apart from these special and broader variations we quickly learn that every individual reacts a little differently from every other individual to adverse as well as to beneficient physical and psychic stimuli . . . For this reason the physician must ever be developing his understanding of human types and reactions."

We can discern in this passage several perceptive observations. First, individuals differ constitutionally from one another. Second, individuals differ in the way they cope with or react to environmental stresses. Third, individuals may be grouped into various biotypes according to the way they react to physical and psychic stimuli, according to their liability to certain diseases. Our two threads —organism and environment—are thus here and somehow they interrelate so as to predict the probable health experiences of an individual.

I have introduced two words—health and disease—that I should define, for I shall use them frequently in this discussion. "Health" is an illusive concept

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A lecture in series on "Natural History of Disease" presented to the first class of freshmen, Rush Medical College, Chicago, Illinois, October 25, 1971

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which only recently has begun to receive the attention it deserves. Although I have attempted to define health myself, I find Audy's[2] definition the better. According to him: "Health is a continuing property, potentially measurable by the individual's ability to rally from insults, whether chemical, physical, infectious, psychological, or social." In the context of this concept of health, disease is "an expression of the rallying, the coping process . . ." Thus there may be degrees of health. Only in death is one unhealthy.

To illustrate the complexity of the dynamic relationships of organism and environment in predicting the health experiences of a population, let us examine an actual health experiment. Dr. L. E. Hinkle, Director of the Division of Human Ecology at Cornell Medical Center, has studied the continuity of patterns of illness and the distribution of sickness disability among healthy adults employed by the American Telephone and Telegraph Company and the New York Telephone Company. His studies,[3] encompassing twenty years of medical observation, revealed that the risk of illness was not distributed evenly among these workers. A small group of individuals consistently accounted for a large proportion of illness in the working populations. Over the twenty-year period, 10 percent of the individuals accounted for 25 percent of the illness, and 50 percent of the individuals accounted for 75 percent of the illness. The 10 percent most frequently ill experienced 34 percent of the total sickness disability, and the 10 percent least frequently ill, only 1 percent. After examining the medical records of these workers, Hinkle et al.[4] concluded that the most reliable predictor of future health experience was the past medical record. Hinkle did not identify why certain individuals experienced more sickness disability than others, but he did observe that "there is a very significant relation between a man's evaluation of his life situation, his reaction to it, and the number of illnesses he experiences." He hypothesized "that a man reacts to his social environment as he perceives it."[5]

According to these observations of Hinkle and his colleagues, there is something about the interactions of organism and environment that distorts the distribution of risk of illness within a population. As a consequence some individuals have a high level of health, others have a low level. Because the nature of individuality has been relatively neglected by human biologists, I shall focus on the thread "organism," particularly human biological variability, and show you how it might relate to the skein you have yet to formulate.

Human Variation

The individual human being can be characterized in terms of an immense array of separate traits—anatomical, biochemical, functional, and behavioral. Each of these traits can be measured with reasonable precision. When a representative population is sampled and the separate traits are measured, it is found that the measurements distribute themselves normally or lognormally.[6] Accordingly, the variance arising from differences between individuals, i.e., interindividual variance, can be expressed by one of several statistics, the standard deviation, the coefficient of variation, or the range ratio. The coefficient of variation and the range ratio are generally more useful for comparing interindividual variances of traits because they are dimensionless. The coefficient of variation is the ratio of the standard deviation to the mean; it is expressed as a percentage. The range ratio is calculated by dividing the maximum value of a distribution of measurements by the minimum value. Customarily before this calculation is made the upper and lower 0.5 percent of the measurements are discarded. Thus the range ratio represents the variance for 99 percent of the population.

When arrays of variances for separate biological traits are examined, an orderliness is soon evident. I have identified this feature of human biological variation

as the *hierarchy of variation.* Among the first scholars to report a hierarchy of variation among human biological traits was Wechsler.[7] He studied the range ratios for 89 biological traits. When he plotted the frequency distribution of the ratios, he found that it was polymodal. The traits arrayed themselves into three groups, those with small, intermediate, and large ratios. I have summarized this observation in Table 1.

TABLE 1

MEAN RANGE RATIOS FOR VARIOUS HUMAN BIOLOGICAL TRAITS*

Groups of Traits	Number of Traits	Mean Range Ratio
Body temperature	3	1.03
Linear traits	13	1.30
Metabolic rates	18	1.39
Body circumference	5	1.52
Physiological functions	6	2.07
Motor capacities	13	2.23
Weight of body and organs	10	2.33
Perception and intellectual abilities	7	2.58

*From Wechsler (Ref. 7, p. 56).

According to Wechsler's observations, there is low variance for body temperature, intermediate variance for measurements of anatomical characteristics, metabolic rates, and physiological functions, high variability for behavioral traits.

Some years ago Mrs. Weinman and I[8] studied the inter-individual variation of 85 traits measured in more than 200 young men. The traits were assigned to three groups: (1) chemical properties of the internal environment, (2) physical properties of the internal environment, and (3) functions of organs and systems. Figure 1 illustrates the polymodal distribution of these 85 traits. According to these observations, there was much less variability among chemical and physical properties of the internal environment than among those traits related to the functioning of organs and organ-systems.

This hierarchy of variation bespeaks a precision of regulation among these organismic traits. Indeed, this precision of regulation is exactly that predicted by the doctrine of physiological regulations. Those traits most essential to the normal functioning of cells should be most closely guarded, i.e. exhibit the least variability. Traits not so essential for the functioning of cells should be less closely guarded. Organs and organ-systems which comprise the internal regulatory mechanisms should exhibit greater variability, and behavioral traits which comprise the external regulatory mechanisms should exhibit the greatest variance.

It follows from the doctrine of physiological regulations that properties of the internal environment most closely regulated should include serum osmolarity, hydrogen ion concentration, core temperature and the concentrations of such electrolytes as sodium, potassium, calcium, and chloride. Properties less closely regulated should include metabolic intermediates, waste products, and serum enzymes.

The coefficients of variation of 13 chemical properties of the blood of healthy young men reveal a hierarchy which agrees closely with the doctrine of physiological regulations. This hierarchy is exhibited in Figure 2. Properties showing the smallest variance are serum sodium, serum chloride, serum osmolarity, hematocrit, serum calcium, and serum potassium. The largest variance is exhibited by serum cholesterol, serum ketone bodies, and the serum enzymes, alkaline phosphatase and amylase.

Comparable observations recently have been reported by Morimoto and his colleagues.[10] The hierarchy of Figure 3 is comprised of mean values for intra-individual variance measured on three subjects during the winter and summer seasons. Values have been ranked according to the annual means for each of the 23 properties measured. Again we see that functionally essential properties show the least variance, and metabolic wastes and enzymes the most variance.

This hierarchy is not significantly different in the two seasons, winter and summer.

The question may cross your mind, How closely does intra-individual variation correlate with inter-individual

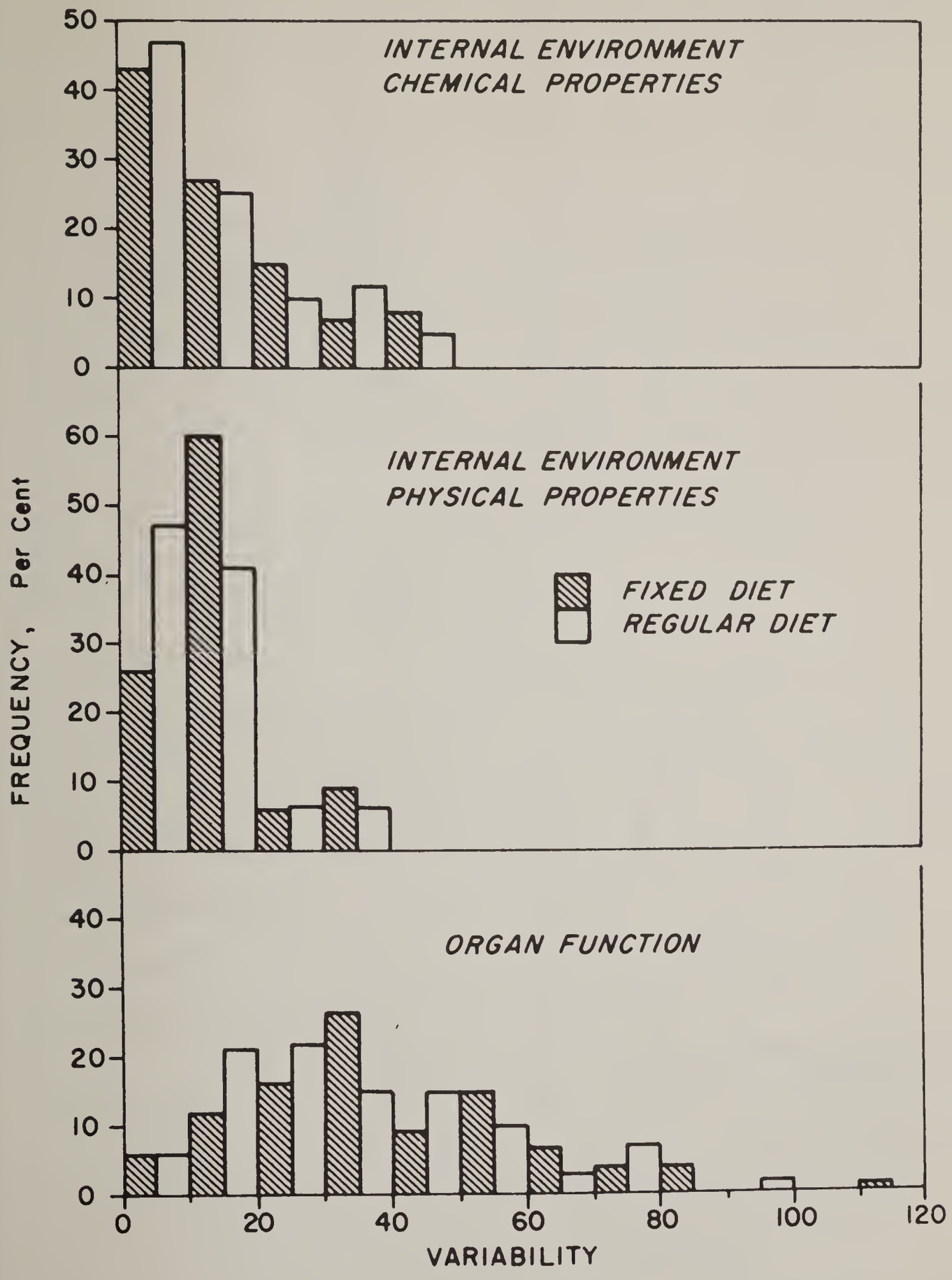

Fig. 1—Frequency histograms for coefficients of inter-individual variation from the chemical and physical properties of the internal environment and the functioning of major organ systems. From Sargent and Weinman.[9] (Reproduced with permission of McGraw-Hill Co. and the authors.)

variation? Can either measure of variance be employed to establish the precision of regulation? Measurements of inter-individual variation made by me and my colleagues[8,9] are compared with measurements of intra-individual variation made by Griffith and Pucher et al.[11,12] and Morimoto et al.[10] in Figure 4. Comparisons are there made for chemical properties of the internal environment, physical properties of the internal environment, and the functioning of organs.

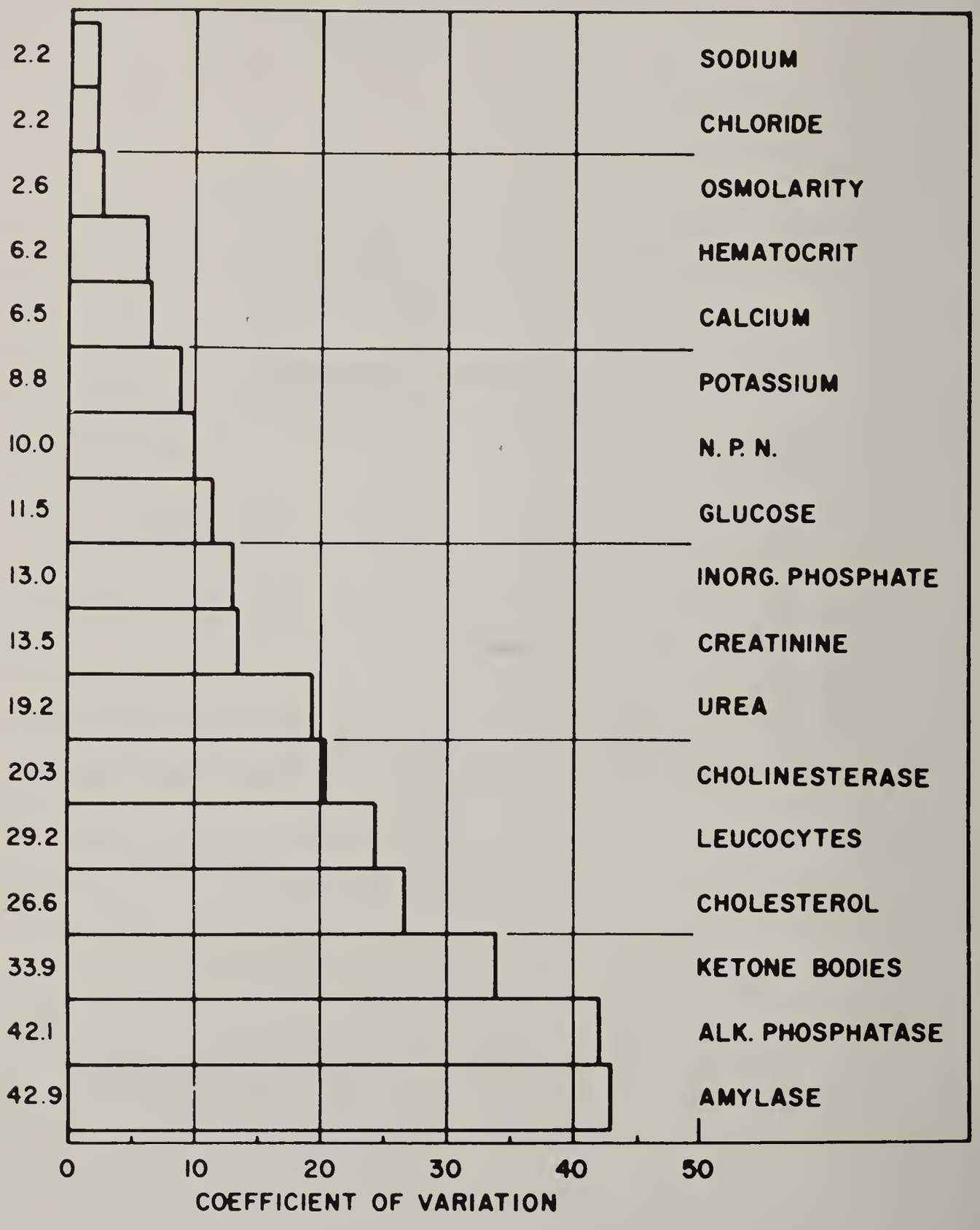

Fig. 2—Ranking of coefficients of inter-individual variation of the chemical measurements of the internal environment. From Sargent and Weinman.[9] (Reproduced with permission of McGraw-Hill Co. and the authors.)

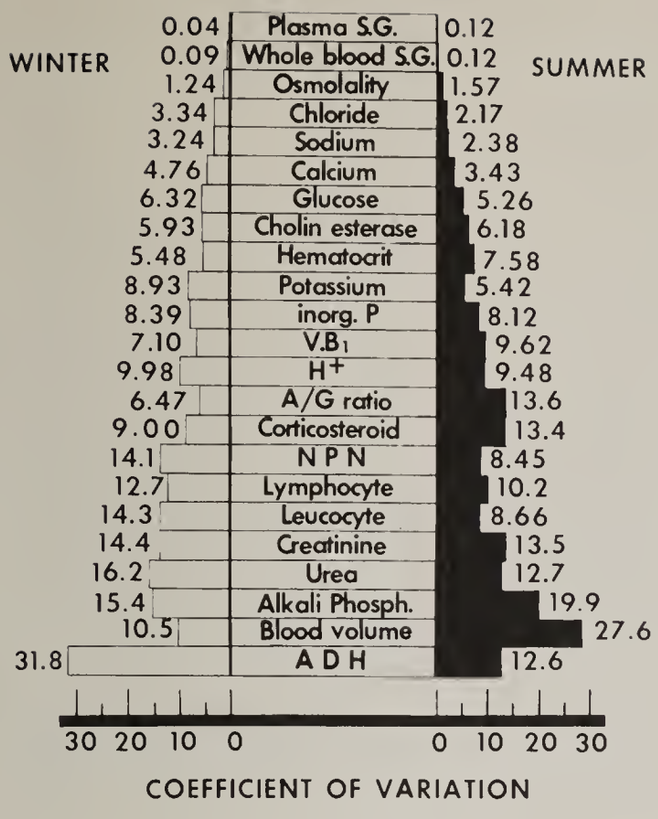

Fig. 3—Comparison of intra-individual variations of internal environment between summer and winter. The items shown in the figure are arranged in the order of magnitude of annual means. (After Figure 1 in Morimoto et al.[10])

Whereas intra-individual variation tends to be smaller than inter-individual variation, both measures reveal the hierarchy of variability which I have identified as precision of regulation. The correlation coefficient is $+0.886$ ($P<0.001$).

When the organism is faced with the task of coping with environmental insults, it should respond so as to protect the internal environment, the composition of which is so essential to the regular functioning of the cells. This deduction follows from the doctrine of physiological regulation and the concept of health. Thus when exposed to external stresses, the organism should react so as to allow smaller changes in the closely regulated properties of the internal environment than in the less precisely regulated properties. The magnitude of change provoked by environmental insults should be a measure of the effectiveness of physiological regulation. Under this deduction there should be a correlation between effectiveness and precision of regulation.

When more than 200 young men were abruptly exposed to conditions simulating threat to survival, it was found that the changes measured in the physical and chemical properties of the blood were highly correlated with the inter-individual variance for these same properties (Figure 5). The rank-order correlation coefficient for a group studied in the winter was $+0.60$ and for a group studied in the summer, $+0.78$.

Morimoto and his colleagues[10] evaluated the effectiveness of regulation of three subjects who had to cope with two stresses: an abrupt exposure to heat in a climatic chamber, and the progression of seasons. A high degree of correlation occurred between the magnitude of intra-individual variation and the magnitude of change provoked by heat stress (Figure 6) and the change provoked by the progression of the seasons (Figure 7).

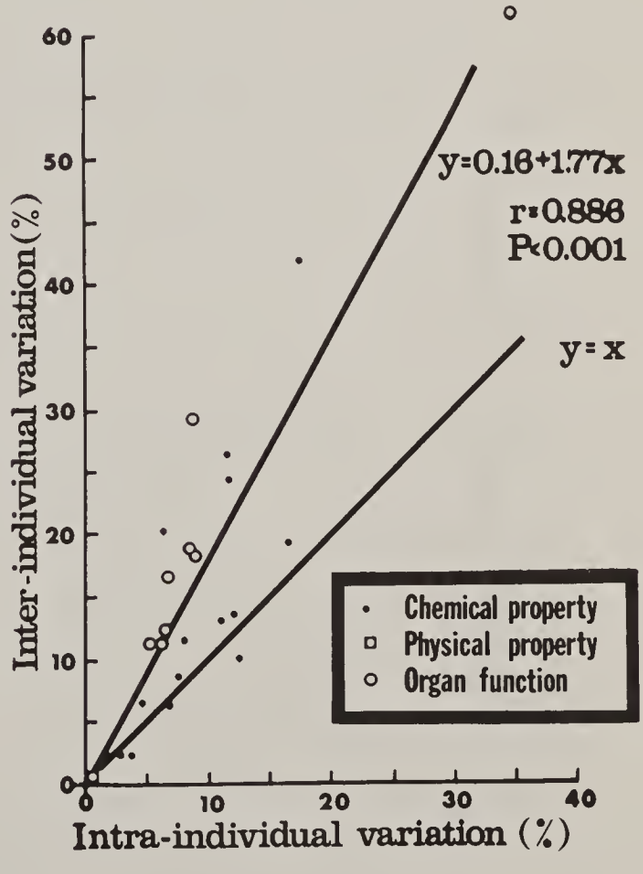

Fig. 4—Comparison of inter- and intra-individual variability. Data collected from publications cited in text.

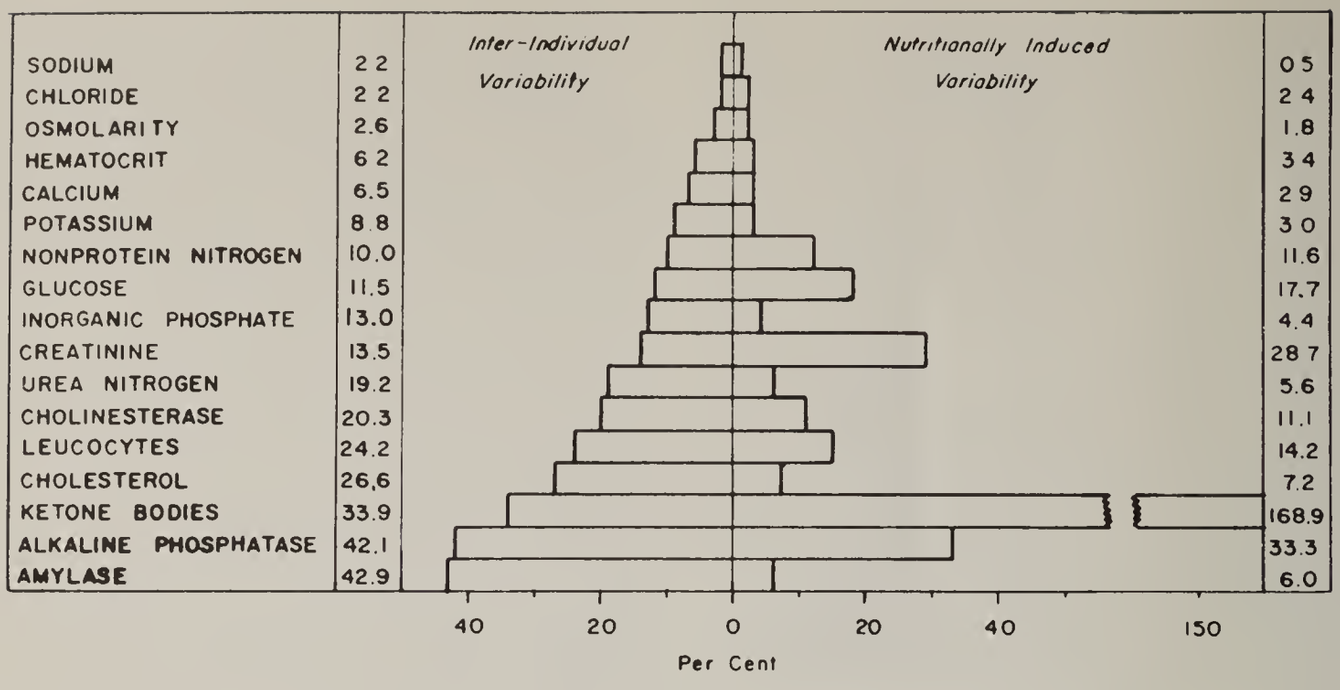

Fig. 5—Effectiveness of physiological regulation: a comparison of the inter-individual variability and the nutritionally induced variability of 17 chemical properties of the internal environment. (After Figure 3 in Sargent and Weinman.[8])

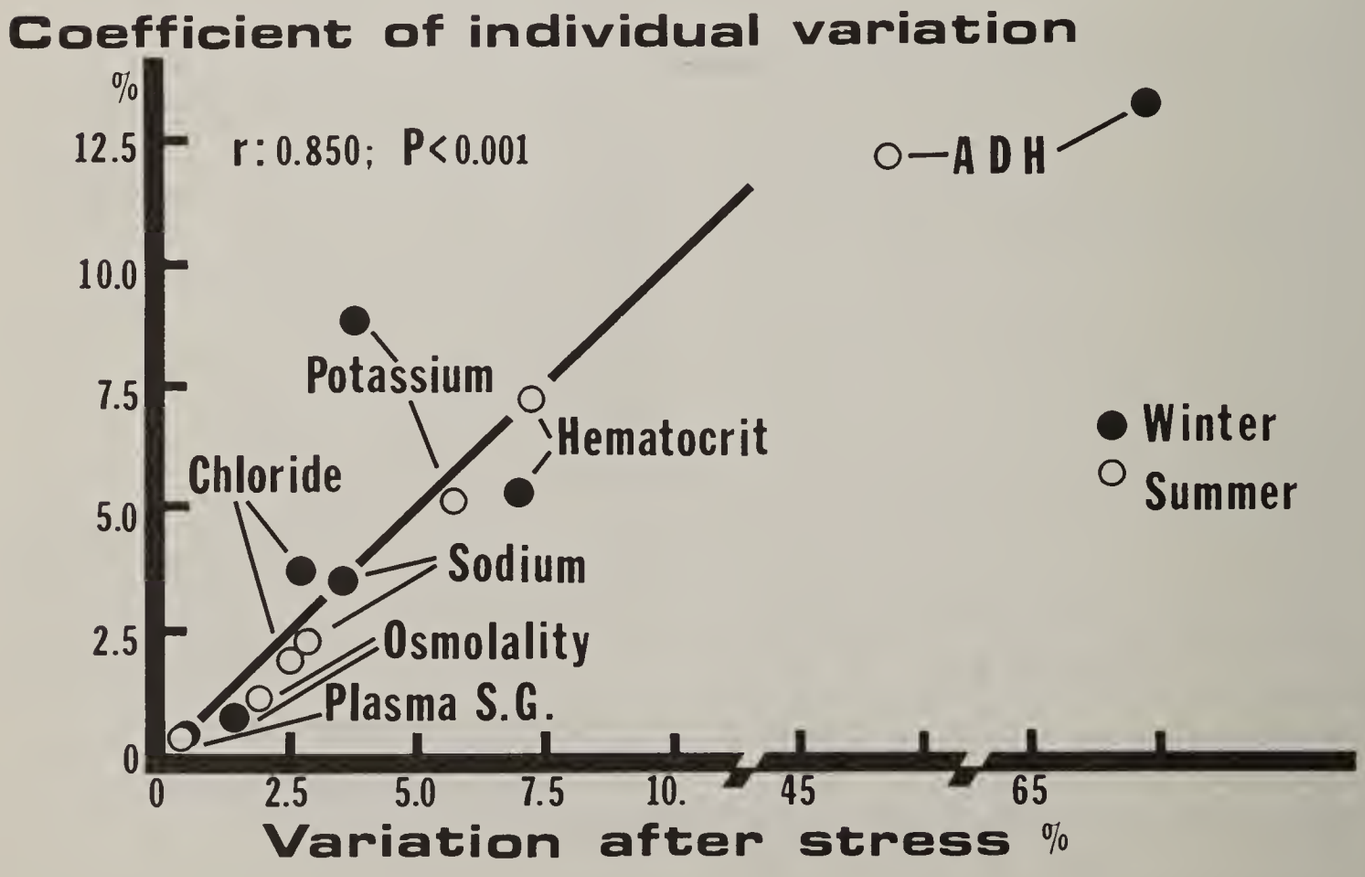

Fig. 6—Correlation between coefficient of individual variation and variation after stress. (After Figure 6 in Morimoto et al.[10])

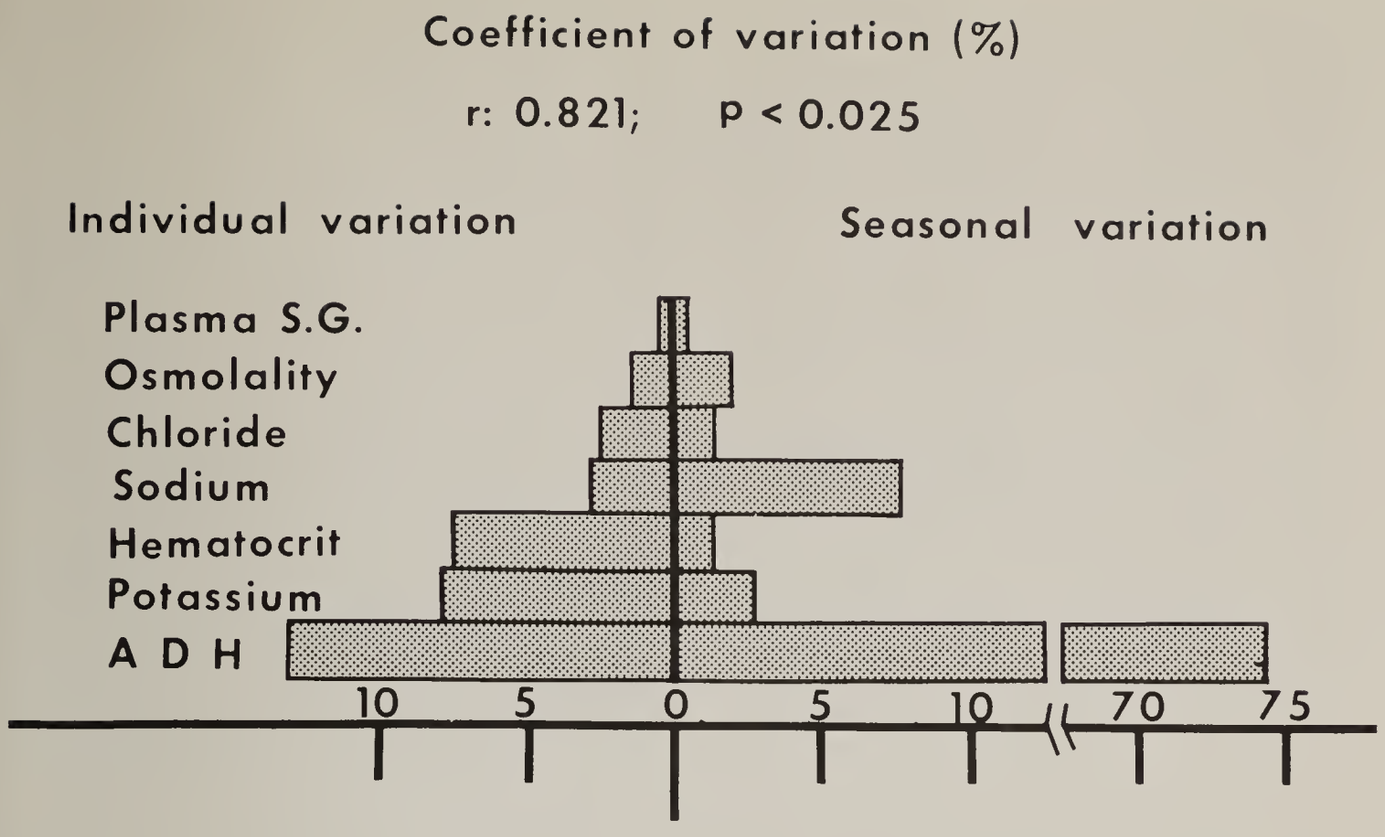

Fig. 7—Comparison between the magnitude of individual variations and seasonal variations. (After Figure 7 in Morimoto et al.[10])

These observations confirm the deduction that there is a close correlation between precision and effectiveness of regulation. They provide considerable insight into the processes whereby the organism copes with environmental insults to maintain health.

Individuality

Up to this point we have been examining the magnitude and regularity of human biological variation. This overview had served to provide a baseline from which to evaluate individuality.

Each individual human being is genetically unique. Inborn differences between individuals express themselves in several ways: inborn errors of metabolism, inherited disease, polymorphic variations, or metrical inheritance (i.e. normal or log-normal distribution of single traits). Because of the continuous variation in the intensity with which a single trait shows itself in a population, it becomes most difficult, with the diversity of human biological variations, to identify individuality on the basis of quantitative differences between individuals when they are studied trait by trait.

Actually inborn differences are combinational. The individual is a unique configuration of physical-chemical, functional, and behavioral traits. Medawar[13] observes, "One individual differs from all others not because he has unique endowments but because he has a unique combination of endowments." The same thought is expressed in Wechsler's "configurational theory of human abilities."[7] According to this theory, when certain critical differences in the intensity of traits have been attained, a new configuration results. Small differences between individuals become meaningful when judged as configurations or combinations of traits that produce new qualitative phenomena. When considered trait by trait, small differences are difficult to evaluate. Speaking to this point, Williams[14] calculates that if one sets two standard deviations as the limits of normal, then only 0.59 percent of the population will be normal for a configuration of 100 traits.

Individuality itself thus should be exhibited in combinations or patterns of traits. In Figure 8 we display the patterns of 16 biochemical traits measured in 12 healthy young men. Each pattern is distinctive. In Figure 9 we display the patterns of 13 tests of organ function measured in the same 12 young men. In Figure 10 we display the energy-balances of 12 young men studied by Edholm et al.[16] Note that whereas the group was in energy-balance over the two weeks of observation, some men were in negative energy balance and others were in positive energy-balance. In none were there significant changes in body weight during the two weeks of study.

Distinctive patterns of individuality persist through time. I studied eight young men who were repeatedly exposed four or five times to physical work in a climatic chamber maintained at a corrected effective temperature of 31° C.[8] Each exposure lasted six to eight hours. The interval of time between exposures was 10 to 21 days. Figure 11 shows the patterns of thermoregulatory responses for the individual subjects. The central line depicts the mean response, and the upper and lower lines depict the extreme values measured. Each individual has a distinctive reaction pattern. Because the lines of the extremes parallel the mean line, we can deduce that the patterns persisted over the 40 to 105 days of observation.

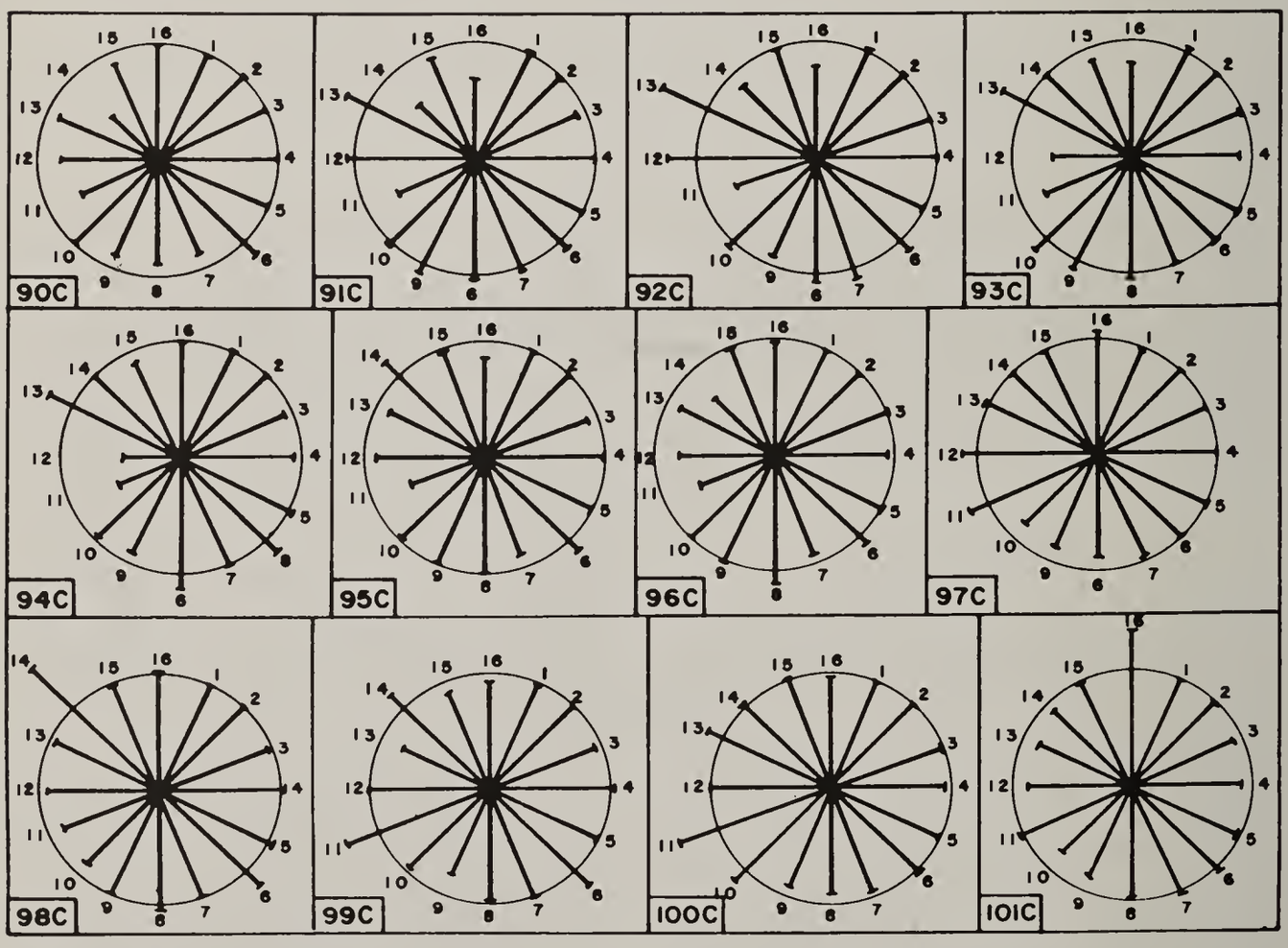

Fig. 8—Individual patterns of chemical properties of the internal environment for 12 subjects on a regular diet in the winter. Numbers at ends of radial lines stand for the following blood measurements: serum osmolarity (1), serum sodium (2), serum potassium (3), serum calcium (4), serum chloride (5), serum inorganic phosphate (6), serum nonprotein nitrogen (7), serum creatinine (8), whole blood glucose (9), serum cholesterol (10), serum ketone bodies (11), serum cholinesterase (12), serum amylase (13), serum alkaline phosphatase (14), hematocrit (15), and total leucocyte count (16). (After Figure 9 in Sargent and Weinman.[8])

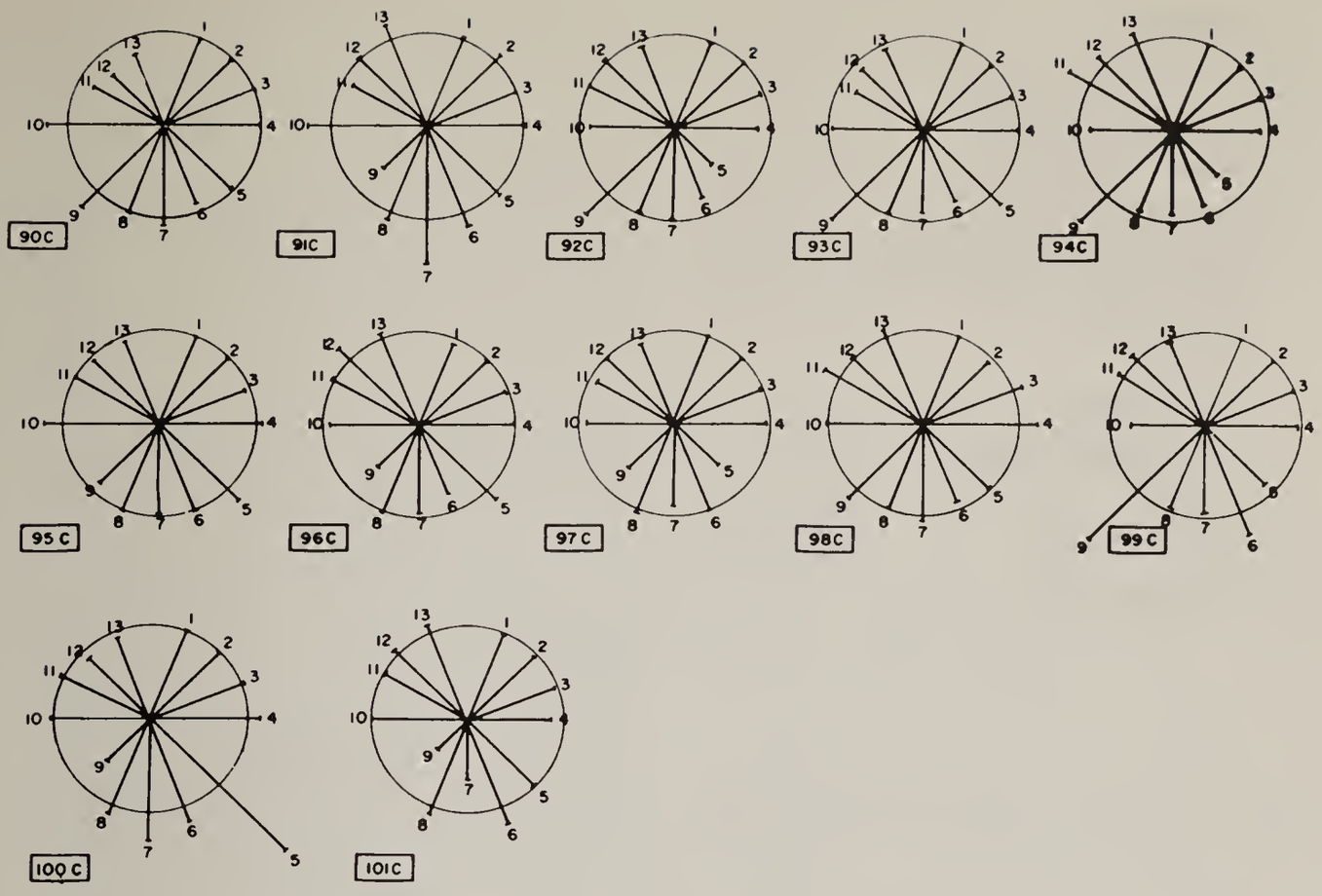

Fig. 9—Individual patterns of organ function for 12 subjects on a regular diet in the winter. Numbers at ends of radial lines stand for the following measurements of organ function: resting systolic blood pressure (1), resting diastolic blood pressure (2), resting pulse pressure (3), resting pulse rate (4), resting minute urinary excretion (5), creatinine clearance (6), osmotic clearance (7), urinary pH (8), urinary titratable acidity (9), resting pulmonary ventilation (10), and passage of time—20 seconds (11), 45 seconds (12), and 70 seconds (13). (After Figure 11 in Sargent and Weinman.[8])

Typology

When one examines a population of humans, one witnesses continuous variation from person to person of any trait that is measured. For centuries physicians have attempted to bring some order to this complex array of differences. Two questions have been asked over and over. Are there constellations of traits that allow the grouping of individuals into types? Is there any association between type and health experience, occupational preference, ability, behavior, etc.? Typology—the search for types—has concentrated on constellations of morphological traits, e.g.; body build, habitus, and somatotype. The search for relations between type and health experience is constitutional medicine, e.g., the sthenic body build is prone to schizophrenia; the ectomorph inclines to hypertension. Neither search has been productive[17] and it is with some trepidation that I tackle the issue yet again.

The classical concept of types was founded on the assumption that there was close integration of bodily traits. Close integration suggested high correlations of traits. The facts are, however, that the correlations between human biological traits are surprisingly low or weak. Some illustrative data from the literature[18-20] are shown in Table 2. The coefficient of determination expresses the fraction of the variance accounted for by the correlation. Note that these coefficients range from a low of zero to a high of only 31 percent! Even though many of the "r's" are statistically significant (these are marked with an asterisk), not much of the variance is explained by the correlation.

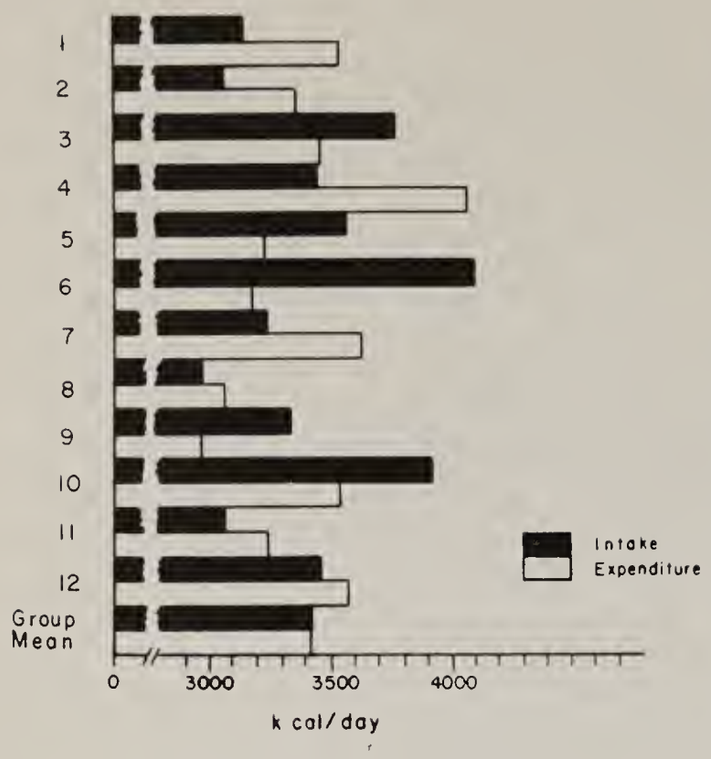

Fig. 10—Individual variations of caloric balance among 12 young cadets (fortnightly means). (After Figure 6 in Sargent.[15])

At first sight these low correlations are surprising when viewed against the concept of homeostasis. On further analysis, the fact that bodily traits do not correlate closely is really not surprising. High correlations would be incompatible with life. "In the presence of very high correlations between all bodily structures and functions," writes Schneider,[17] "even a minor derangement would result in the disruption of the total system." Actually the body functions as though it were comprised of a series of autonomous subsystems each separated from the others by intraorganic barriers. The blood-brain barrier is an example. Variations in the blood bear little or no relation to variation in the spinal fluid. As Schneider emphasizes, "In reality, the remarkable autonomy of the 'subsystems,' attested by some of the low or zero coefficients of correlation, accounts for the fact that the

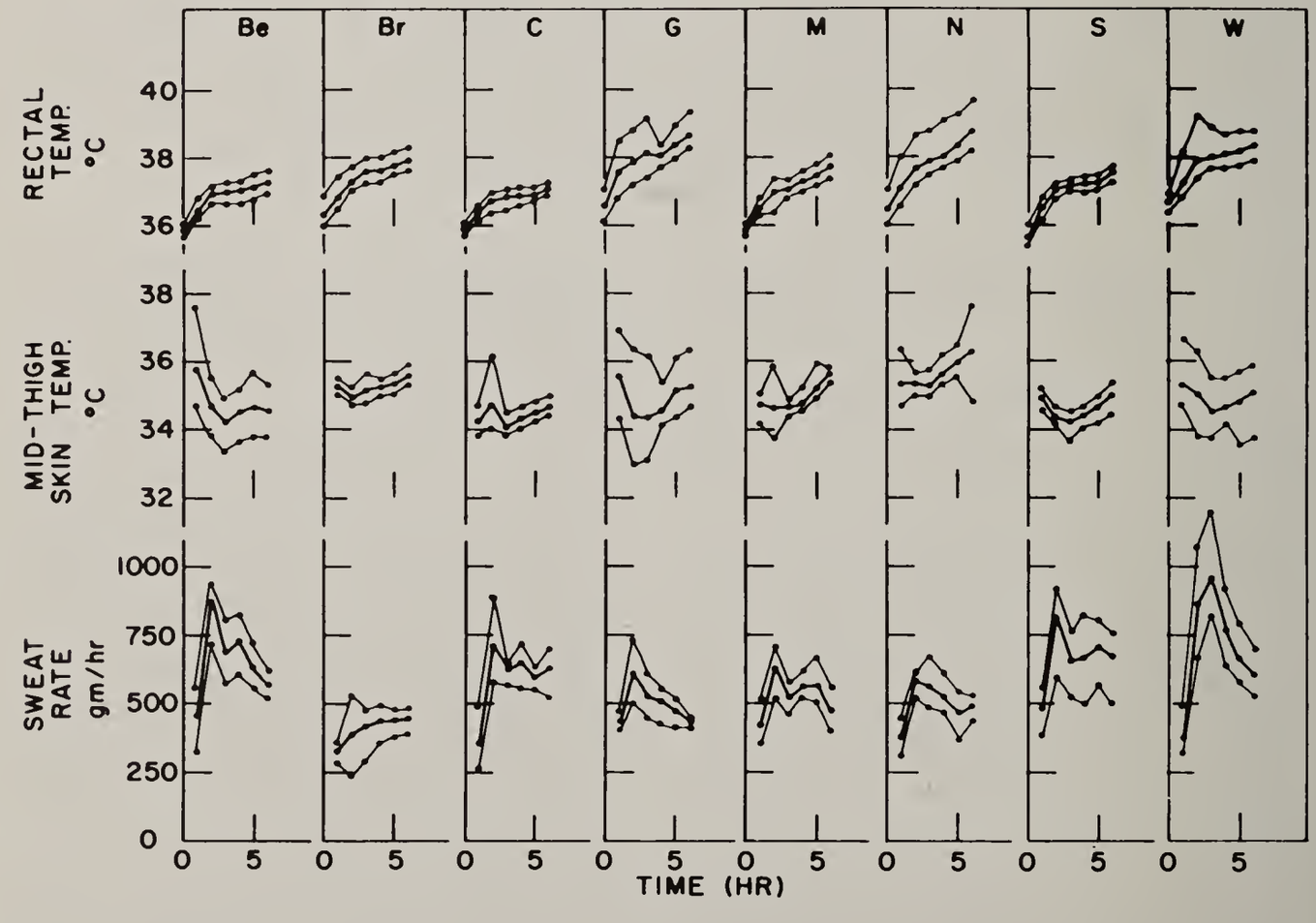

Fig. 11— Individual patterns of thermoregulatory response to marching 5.6 km/hr on level treadmill in atmospheric environment of 31°C, corrected effective temperature. Data for eight different subjects shown: middle lines represent mean hourly values; other lines represent extreme hourly values; O stands for resting period. (After Figure 17 in Sargent and Weinman.[8])

majority of circumstances remain localized."

Disconformities

Some individuals in a population exhibit traits that deviate markedly, by several standard deviations, from the reference mean. That such individuals are not handicapped by these deviations suggests that the deviations are compatible with a healthy, productive existence. In fact the existence of these deviations is not unexpected in view of the fact that traits generally exhibit low correlations. Study of these individuals sheds additional light on the compart-

TABLE 2

ILLUSTRATIVE TRAIT CORRELATIONS

Traits	Correlation Coefficient r	Coefficient of Determination r^2
Habitus x Biochemical		
Endomorphy with		
Urinary creatinine	0.49*	0.24
Urinary 17—ketogenic steroids	—0.01	0.0001
Urinary 17—ketosteroids	0.15	0.022
Mesomorphy with		
Urinary creatinine	0.49*	0.24
Urinary 17—ketogenic steroids	0.02	0.0004
Urinary 17—ketosteroids	0.27*	0.078
Ectomorphy with		
Urinary creatinine	—0.44*	0.19
Urinary 17—ketogenic steroids	0.03	0.0009
Urinary 17—ketosteroids	—0.22*	0.048
Biochemical x Biochemical		
Urinary creatinine with		
Urinary 17—ketogenic steroids	0.21*	0.045
Urinary 17—ketosteroids	—0.42*	0.18
Serum albumin with		
Serum calcium	0.40*	0.16
Serum magnesium	0.11*	0.012
Serum inorganic phosphate	0.12*	0.014
Serum urea	—0.005	0.000025
Serum protein	0.56*	0.31
Serum alkaline phosphatase	0.01	0.0001
Physiological x Biochemical		
Systolic blood pressure with		
Serum albumin	0.35*	0.12
Serum cholesterol	N.S.	N.S.
Diastolic blood pressure with		
Serum albumin	0.17	0.029
Serum cholesterol	0.26*	0.067
Urinary volume with		
Urinary creatinine	0.21*	0.045
Urinary 17—ketogenic steroids	0.45*	0.20
Urinary 17—ketosteroids	0.48*	0.23

*Correlation coefficient statistically significant: P at least less than 5%

mentalization of physiological regulations.

Williams[21] defines widely deviant traits as disconformities. He proposes that a trait disconforms when it deviates by more than three standard deviations from the reference mean. When individuals persistently exhibit deviations of several traits which differ from the reference means for the same traits by one or more standard deviations, we suggest that such individuals be identified as multiple disconformers.

Mrs. Weinman and I[8] examined the records of 23 young men who had subsisted on a regular diet for six weeks and who were repeatedly subjected to a battery of tests that measured biochemical properties of their blood and the functioning of their organs. Our plan was to identify subjects showing persistently deviant measurements and then to test the statistical significance of any multiple disconformities.

Two steps, each with statistical control, were followed. The first step was to identify individuals who differed qualitatively from the group with respect to either measurements of biochemical properties or organ function or both. The second step was to evaluate quantitatively the nature and magnitude of the deviations exhibited by these individuals.

Three individuals were found whose biochemical properties ranked significantly high (92C) or low (90C, 91H) by the Chi-Square test (Figure 12). Four other individuals had organ functions ranking significantly high (94H) or low

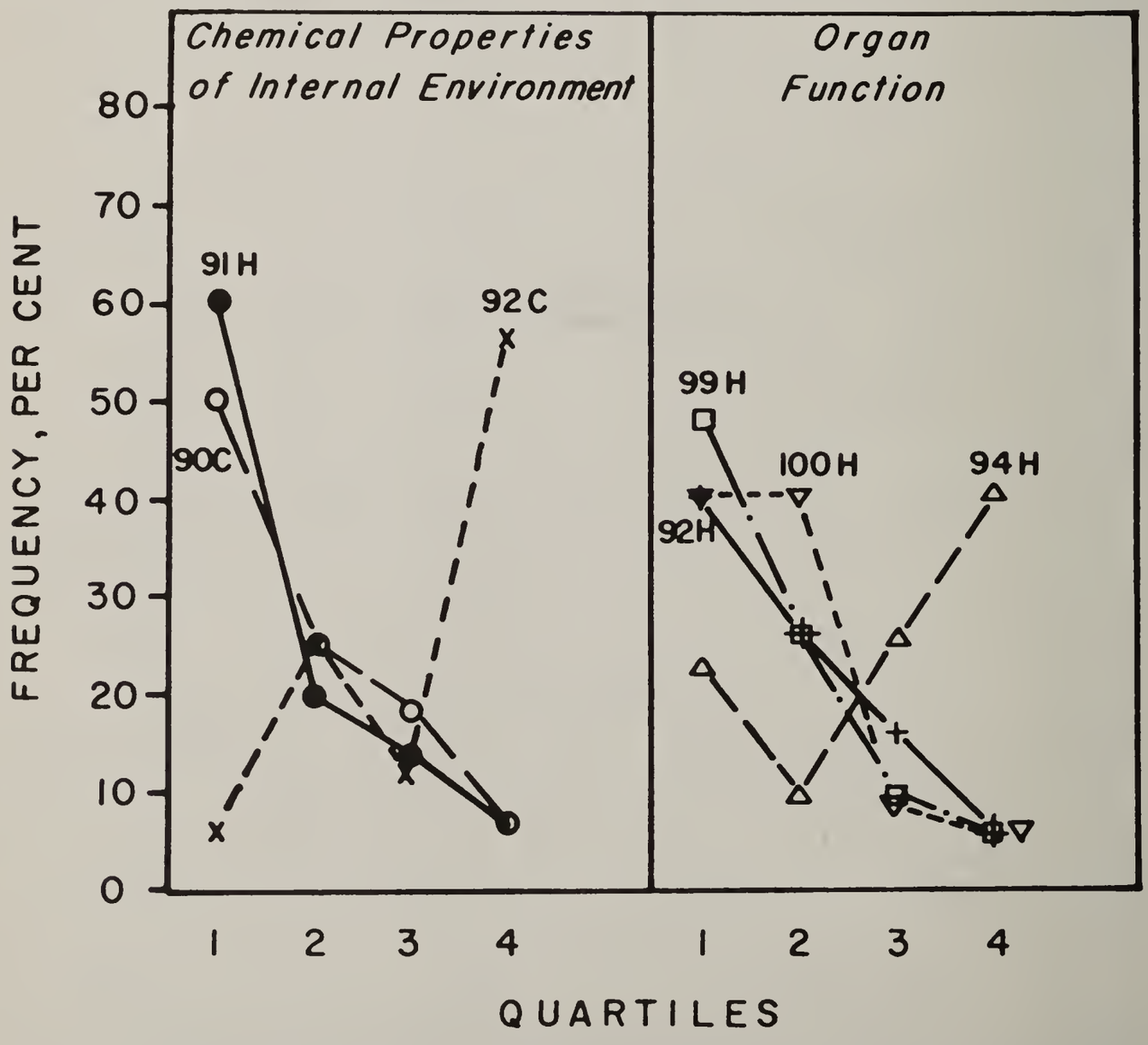

Fig. 12—Quartile frequency distributions of measures of chemical properties and of organ function for subjects ranking significantly high or low for these traits ($P < 0.05$ by X^2 test). (After Figure 14 in Sargent and Weinman.[8])

(92H, 99H, 100H) (Figure 12).

The most significant fact revealed by these data is that no individual was deviant for both biochemical properties and functioning of organs. This fact suggests that an individual may inherit deviant organ functions and have average biochemical properties of the internal environment, or he can inherit average functions of organs and exhibit deviant biochemical properties. The ends and means are independent insofar as the genetics of homeostasis is concerned.

The biological traits of these seven subjects were examined. If five of the six measurements of any trait differed from the group mean for that trait, it was tabulated. The magnitude of deviations of these traits was measured in standard deviations.

Each of the seven subjects proved to be a multiple disconformer (Figure 13). The observed accumulated percentages for the deviant traits were compared with the expected percentages. Beyond the class interval of one sigma, the accumulative percentages approached 90 to 95 percent while the expected percentages approached 50 percent. For chemical traits no deviation exceeded four sigma; for organ function none exceeded six sigma.

These biometrical exercises demonstrated a lack of correlation among constellations of traits. Disconforming biochemical properties did not occur in individuals with disconforming organ functions nor did disconforming organ functions occur in individuals with disconforming biochemical properties. No individual was a disconformer in both chemical properties and organ functions.

The Concept of Subsystems

If the concept of autonomous subsystems is valid, one would expect to find higher correlations among traits within a subsystem than between subsystems.

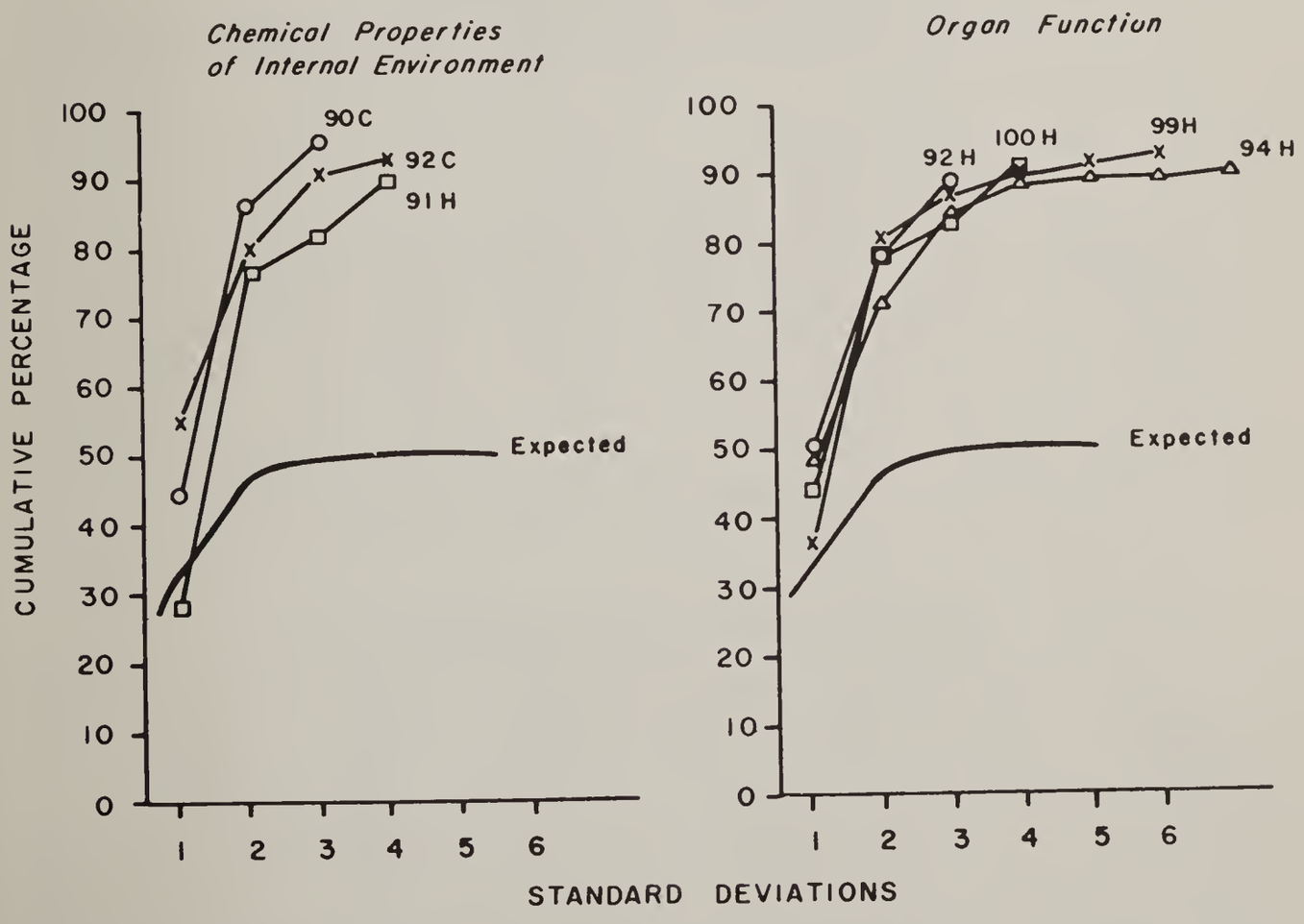

Fig. 13—Multiple disconformities of biological traits (chemical properties of internal environment or organ function) for seven subjects represented as cumulative frequency distributions of differences from group means measured as standard deviations. Line of expected percentages calculated on basis of "normal" distribution for differences. (After Figure 15 in Sargent and Weinman.[8])

There is some evidence supporting this deduction. Among various subsystems that might be hypothesized are those subserving separate vegetative functions, e.g., digestion, respiration, transport, transformation, utilization, storage, blood-buffering, excretion, etc. The separate traits comprising a discrete vegetative function would be more closely correlated than separate traits representing different vegetative functions.

Two examples from the literature will serve to illustrate this thesis. Some data on the fat transport system[22] are shown in Table 3. Note the high coefficients of correlation between the separate traits. In Table 4 we show some data on iron transport.[23] The matrix has been divided into four quadrants. The traits segregated in the lower right quadrant can be assigned to the iron transport subsystem. Note the high correlation coefficients. The traits segregated in the upper right quadrant are not specifically related to iron transport. Note the low correlations between these traits and those specifically related to iron transport.

Organismic Unity

If organisms are indeed made up of relatively autonomous subsystems, how then is organismic unity achieved? It is a fact that organisms function as holistic units. This unity is provided by the central and autonomic nervous systems and by the endocrine system. The subsystems may be viewed as targets for the actions of nerve impulses and hormones.

Bio-environmental Constellations

If we accept the concept that health of an organism expresses itself as the

TABLE 3

CORRELATION MATRIX FOR LOW DENSITY LIPOPROTEINS AND SERUM LIPIDS IN NORMAL MALES: FAT TRANSPORT

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
(1) Sf 0-10^5	—							
(2) Sf 20-10^5	0.82	—						
(3) Sf 0-20	0.63	0.07*	—					
(4) Total lipid	0.96	0.80	0.58	—				
(5) Triglycerides	0.82	0.99	0.08*	0.82	—			
(6) Total cholesterol	0.73	0.30**	0.86	0.77	0.32**	—		
(7) Phospholipids	0.82	0.54	0.68	0.90	0.57	0.90	—	
(8) A.I. Δn	0.97	0.94	0.41	0.94	0.94	0.57	0.73	—

*Not significant
**$P < 0.05$
Others $P < 0.01$

TABLE 4

CORRELATION MATRIX FOR IRON TRANSPORT AMONG HEALTHY ADOLESCENT MALES

	(1)	(2)	(3)	(4)	(5)	(6)	(7)
(1) Hemoglobin	—	0.71*	0.54*	0.08	0.03	0.07	0.10
(2) Hematocrit		—	—	−0.02	0.15	0.14	—
(3) MCHC			—	0.16	0.12	−0.04	—
(4) Serum iron				—	0.36*	0.17	0.90*
(5) UIBC					—	0.86*	−0.57*
(6) TIBC						—	−0.11
(7) % Sat. TIBC							—

*$P < 0.01$

capacity to cope with environment, then it follows that typology should concern itself not with organism in isolation but organism in environment. Typology should seek to identify bio-environmental constellations that predict the probable health experiences of the life sequence. This deduction is reasonable, for not only is the organism unique but its life sequence is also unique. Although persons share life experiences, their perceptions, interpretations, and implications are personal and singular. We have already noted, for example, that a man reacts to his social environment as he perceives it. It is not unexpected then to find that in recent years, physicians studying typology have begun to identify bio-environmental constellations that correlate with health experience. We shall examine two by way of illustration.

Heat Disease. An illness which distresses populations in the midwest during a summer heat wave or southern military posts where recruits are given basic training is heat disease, particularly heat stroke. Intensive studies have been conducted during the past three decades to identify the predisposing traits. Two have been consistently noted: overweight or obesity and lack of heat acclimatization.[24] Both these traits are organismic but both also represent an organismic-environmental interaction. Obesity is not uncommonly a sign of over-eating, positive calorie balance. Obesity is also an expression of a body type; the pyknic or the ectomorph are obese individuals. Lack of acclimatization represents absence of recent experience with hot weather.

Coronary Thrombosis. Coronary thrombosis is an illness which Dr. William B. Kannel, Director of the Framingham Study, describes as epidemic.[25] For some years the medical teams at Framingham as well as other cardiologists and epidemiologists have sought "to construct the medical profile of the coronary prone individual." The profile that has begun to emerge from these investigations links organism with environment. That is, we deal with a bio-environmental constellation of traits.

I have compiled a list of some of the traits that investigators have listed in the profile of the coronary-prone individual. These traits have been grouped in Table 5 according to whether they are "predominantly organismic" or "predominantly environmental." Although this constellation represents a significant advance over the older constitutional approach, the uniqueness of this constellation is highly controversial. For example, Page et al.[26] on the one hand, claimed to be able to predict with a very high degree of precision the coronary-prone individual from only three of the organismic traits: age, serum cholesterol, and total triglycerides. On the other hand, when Hatch et al.[27] examined ten bio-environmental traits to see how well they discriminated between subjects who had had an attack of coronary thrombosis and matched controls, they found that the traits were not really unique for the victims of coronary thrombosis. The ten traits included height less than 5 feet 8 inches, family history of coronary thrombosis, smoking two packages of cigarettes or more per day, abnormal glucose or cortisone-glucose tolerance test, serum cholesterol more than 210 mg/100 ml, fasting serum triglycerides more than 150 mg/100 ml, abnormal fat tolerance test, pre-β-lipoprotein over 12 units, α_1-lipoprotein under 10 units, and post-heparin lipoprotein lipase under 0.30 Eq/ml/min. The average man with a history of coronary thrombosis fulfilled only five of these criteria. The average control fulfilled two of the criteria.

The situation is no clearer on the environmental side. Friedman et al.[28] have reported that the coronary-prone individual is one who exhibits an excessive sense of time-urgency, preoccupation with vocational deadlines, and enhanced competitive drive. His type A individual is thus subject to chronic stress. Hinkle et al.[29] do not agree. They found evidence of increased risk among men who had high levels of responsibility, or who were promoted rapidly,

frequently, or recently, or who were transferred to new departments or new companies. In this study the risk was particularly high among men who entered the organization without a college degree. This risk existed at the time the men were hired and appeared to be related to socio-economic background rather than to the educational process *per se*. Equally controversial is the role of diet and exercise. Last summer Irving Page,[30] in a perceptive editorial in *Modern Medicine* concluded that both were important and interdependent.

As a final point, look at the correlation matrix of traits in a coronary profile. The data in Table 6 are from a paper by Hatch et al.[27] The correlation coefficients are really no better than the ones we saw earlier. Even though patients and controls are combined, the values approach what one would expect under the hypothesis of autonomous subsystems. The one surprising finding is that the values in the lower right quadrant—values that relate to fat transport—are not as high as those shown earlier in Table 3.

TABLE 5

BIO-ENVIRONMENTAL TRAITS COMPRISING THE PROFILE OF THE CORONARY-PRONE PERSON

Predominantly organismic	Predominantly Environmental
Age	Diet
Heredity	Exercise
Pattern of blood lipids	Toxic agents
Blood pressure	Smoking
Coronary flow	Chronic stress
Carbohydrate tolerance	
Degree of adiposity	
Electrocardiographic abnormalities	
Blood uric acid	
Vital capacity	
Hemoglobin	
Diabetes mellitis	
Lipidosis	

TABLE 6

CORRELATION MATRIX OF TRAITS IN A CORONARY PROFILE

Measurements	1	2	3	4	5	6	7	8	9	10
1. Percent of Ideal Body Weight	—	0.34	−0.06	0.36	—	0.29	0.17	−0.32	0.02	0.22
2. 1-Hr. Blood Sugar in GTT		—	0.25	0.34	—	0.09	—	0.30	0.20	—
3. Serum Cholesterol			—	0.39	—	—	−0.24	−0.06	0.56	—
4. Fasting Serum Triglycerides				—	—	0.47	−0.13	−0.23	0.47	0.10
5. 9-Hr. Triglycerides in FTT					—	—	−0.34	—	—	—
6. Fasting Nonesterified Fatty Acids						—	—	—	—	—
7. Lipolysis K Value							—	0.37	—	—
8. α_1—Lipoprotein								—	0.23	—
9. Pre-β—Lipoprotein									—	—
10. Serum Uric Acid										—

N.B. Underlined values: $P < 0.05$; other values not statistically significant.

Summary

We have taken a look at the subject of human biological variation. We have found that the individual is unique and that it is difficult to classify individuals according to probable health experiences during the life sequence. Some progress could be detected when the constellations of traits were extended to include both organismic traits and environmental experiences.

Why is it so important for the physician to be familiar with human biological variation and with bio-environmental constellations? The physician must devote increasing attention to preventive health maintenance rather than to the alleviation of illness. To accomplish preventive health maintenance he must understand individuality and the meaning of bio-environmental constellations. It is Dr. Kannel's[25] opinion that the day will soon come when the development of disease in a patient under periodic health surveillance will be considered a medical failure.

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VULVAR PRESENTATION OF AN UNUSUAL CARTILAGINOUS LESION OF THE PELVIS

William F. Hejna
Martin G. Schiller

INTRODUCTION

This is a unique cartilaginous lesion reported because of its mode of presentation, the surgical approach used, and its unusual histological picture.

Cartilage tumors of the pelvis must be treated with respect. In Dahlin's series,[1] 30 percent of all chondrosarcomas were found in the pelvis, and he stated that "the nearer a cartilaginous tumor is to the axial spine, the more likely it is to be malignant."[2] Enchondromas are rarely found in this area but are invariably benign when seen. Uncommonly chondroblastomas[3] and chondromyxoid fibromas[4] may arise from the iliac portion of the pelvis. Osteochondromas are also occasionally seen in the pelvic region, but are easily diagnosed radiologically especially when multiple lesions exist. The only other cartilaginous tumor described in the literature is the chondroblastic osteosarcoma.

CASE REPORT

A 55-year-old, white female noticed a painless lump in her perineum two months prior to admission. On vaginal examination, a rubbery, firm, nonmobile, slightly tender, golf-ball-sized mass was discovered in the vulva between the clitoris and urethra. She had no symptoms of dysuria, frequency, radiating pain, or dysparunia. X-rays revealed an unremarkable bony pelvis, with a round soft tissue shadow present directly antero-inferior to the pubic symphysis (Fig. 1).

Excisional biopsy was carried out under general anesthesia with a Foley catheter in place, with the patient in the lithotomy position. An inverted U-type incision was made in the anterior triangle within the pudendal cleft between the clitoris and urethra (Fig. 2). This was deepened by sharp and blunt dissection through the superficial and deep perineal pouches until the mass was exposed immediately anterior to the pelvis (Fig. 3). It was removed from the symphysis pubis sharply and the wound was closed in layers. Great care was taken throughout surgery to avoid traumatizing the internal pudendal artery and its branches (perineal and clitoral) or the pudendal nerve and its branches (perineal and dorsal clitoral nerves). These neurovascular structures course anteriorly from beneath the superficial transverse perineal muscles and do so lateral to the *labia minora*.[5]

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Fig. 1—X-ray of pelvis showing a circular outline of increased soft tissue density anterior to the symphysis pubis. The bony pelvis is normal.

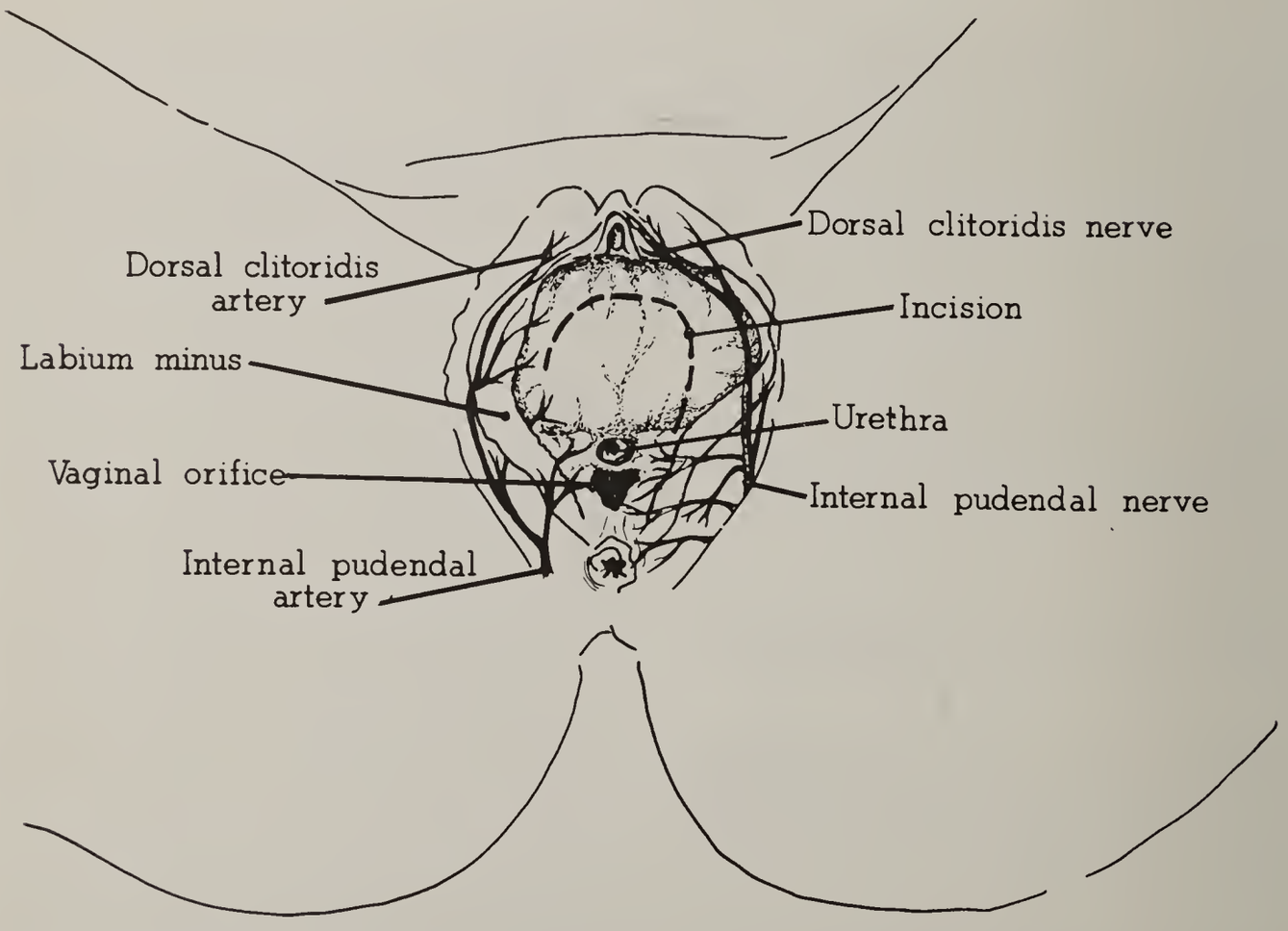

Fig. 2—Diagrammatic view of vulva showing "hockey-stick" type of incision placed well away from the neurovascular supply to the clitoris.

Fig. 3—Photograph of tumor at time of surgery.

Gross examination of the specimen revealed a round tumor which weighed 8 grams, was 4 centimeters in diameter and was greyish-white. It contained a grey paste-like material in its center. Microscopic examination revealed a non-invasive encapsulated mass of fibrocartilaginous tissue with central necrosis (Fig. 4). Areas of myxomatous stroma with peripheral perivascular collections of large stellate cells were noted (Fig. 5). Small calcific deposits were scattered throughout the tissue. Chondrocytes were present (Fig. 6).

DISCUSSION

Definitive histologic diagnosis was controversial among pathologists. One interpretation was that of a low-grade chondromyxosarcoma with a cautionary note that recurrence could be expected if the lesion were not completely excised. Others, however, emphatically maintained that the tumor was not malignant, and probably was not even a neoplasm. It was thus labelled "hyperplastic nodular proliferation of fibrocartilagnous tissue with central necrosis coming from the symphysis pubis." Descriptively it was likened to the proliferative intervertebral disc changes seen in degenerative conditions of the vertebral column.

Sutro[6] reported on the radiological and pathological appearance of the symphsis pubis in 75 autopsy specimens ranging in age from one to over fifty years. He described the degenerative changes in detail and showed that in multiparous females over 50 years of age: (1) the hyaline cartilage is replaced by fibrillated fibrocartilage; (2) clefts form, due to fibrous invasion of the hyaline cartilage by the anterior pubic ligament; and (3) advanced degeneration of the interpubic

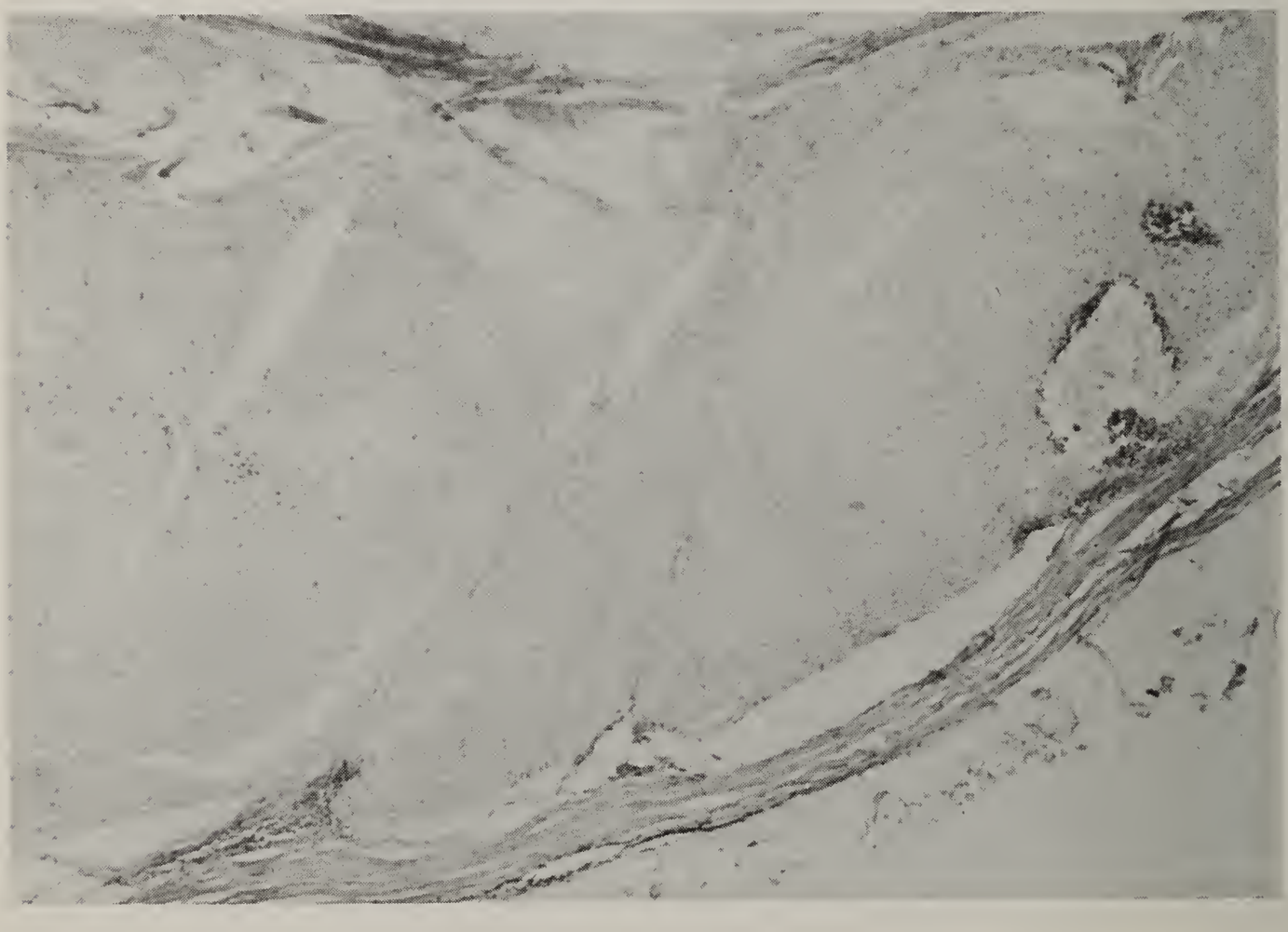

Fig. 4—Photomicrography (50x) showing the encapsulated lesion composed mainly of irregular and degenerated fibrous connective tissue with local collections of large cells.

Fig. 5—Photomicrograph (300x) showing a cellular area composed of polyhedral cells containing several chondrocytes.

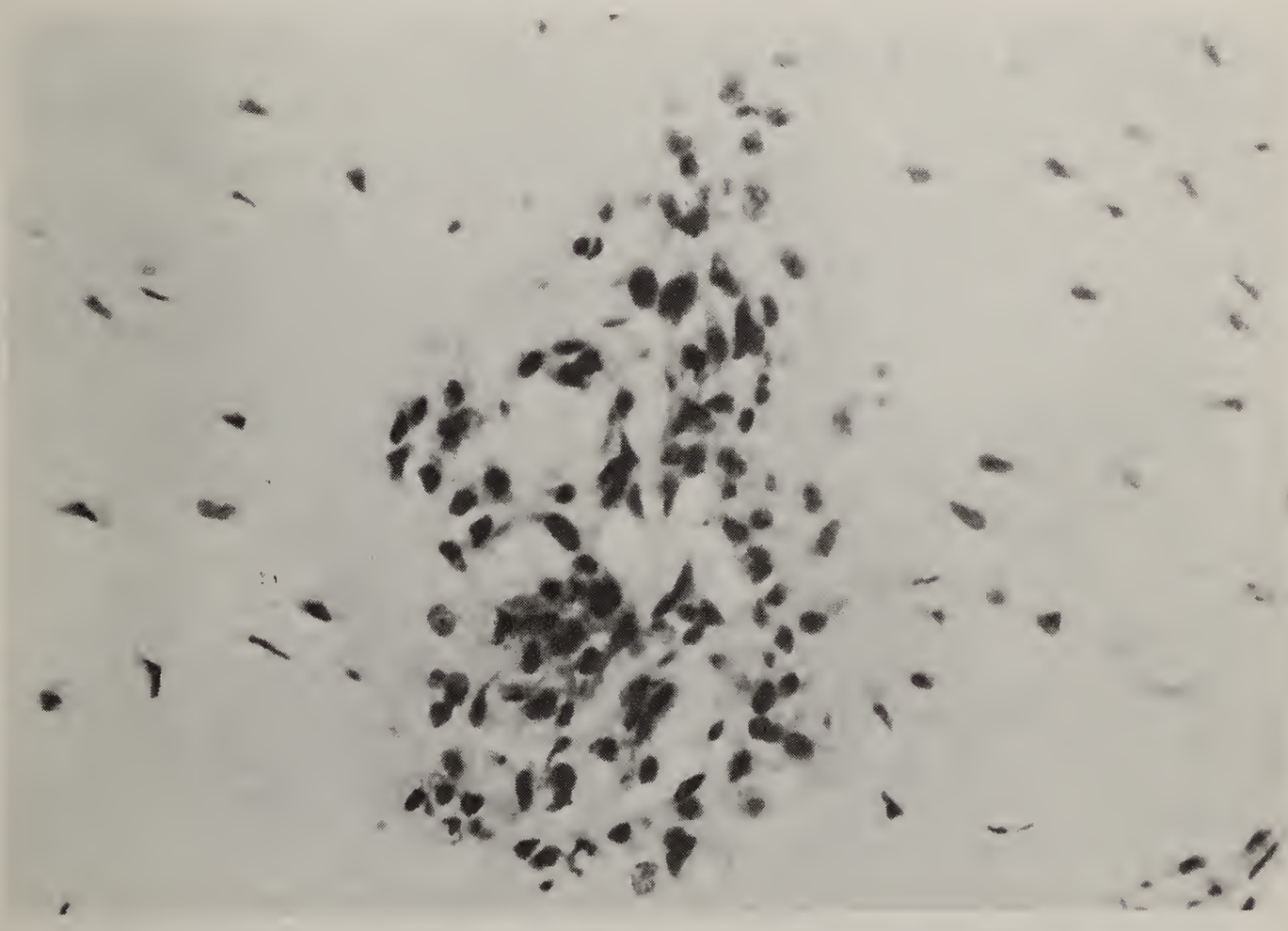

Fig. 6—Photomicrograph (300x) of an area within the tumor showing two chondrocytes in their lacunae surrounded by necrotic cartilaginous matrix.

and anterior pubic ligaments can occur with both islands of live or necrotic cartilage cells and mucoid changes present in the matrix.

On study of the microscopic sections in this case, mature cartilage, giant cells, bone, or osteoid could not be found. Due to areas of myxomatous change adjacent to the degenerated cartilage, some minimal consideration was given to labelling the lesion a chondromyxoidfibroma. These myxoid areas, with their plump stellate cells, suggested low-grade malignancy to some pathologists; however, this was not a prominent aspect of the picture.

By x-ray appearance alone, a diagnosis of any primary cartilage neoplasm of bone is impossible to accept in this case. There were no structural changes seen in the bony pelvis, and no cortex erosion, periosteal elevation, calcification, or lytic areas (Fig. 1). Chondromyxosarcomas of extra skeletal origin may appear in this manner; [7,8] however they are extremely rare.

SUMMARY

It is our feeling that the tumor in the case of this multiparous patient represents degeneration of the pubic synchrondosis with herniation through the anterior pubic ligament. Proliferation of cartilage cells then occurred with central necrosis due to inadequate vascularization. The surgical route utilized for excision was chosen to protect both neurovascular supply to the clitoris, and the urethra.

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ABSTRACTS

OF PUBLICATIONS BY THE STAFF

Biochemistry

Booyse FM, Hoveke TP, Zschocke D, Rafelson ME Jr: Human platelet myosin: Isolation and properties. *J Biol Chem 246:4291-4297, 1971*

A rapid purification procedure for myosin from human blood platelets is described. The isolated protein was found to be homogeneous by ultracentrifugation, free diffusion, and immunochemical criteria. The following physical parameters of the protein were established; sedimentation coefficient ($s^0_{20,\omega}$) 6.8 S; diffusion coefficient ($D_{20,\omega}$) (from boundary spreading during free diffusion), 1.13 $\times$ 10^{-7} cm^2 sec^{-1}; partial specific volume ($\bar{v}$), 0.731 ml g^{-1}; molecular weight, 542,700 g $mole^{-1}$; and frictional ratio (f/f_0), 3.48. The amino acid composition of platelet myosin is reported. Divalent cations such as Ca^{++} and Mg^{++} activated the myosin ATPase activity, whereas EDTA inhibited the enzyme activity. Succinylation of platelet myosin indicated the presence of a large subunit with sedimentation coefficient ($s^0_{20,\omega}$) of 4.9 S. In addition, electron micrographs of two types of negatively stained (uranyl acetate) polymerized platelet myosin (types I and III) are shown.

Booyse FM, Sternberger LA, Zschocke D, Rafelson ME Jr: Ultrastructural localization of contractile protein (thrombosthenin) in human platelets using an unlabeled antibody-peroxidase staining technique. *J Histochem Cytochem 19:540-550, 1971*

Soluble horseradish peroxidase-antihorseradish peroxidase (rabbit) complex was used to localize the actomyosin-like contractile protein, thrombosthenin, in both intact human platelets (Epon-embedded) and ultrathin sections (meth-acrylate-embedded). Antibody staining of ultrathin sections showed the presence of membrane-associated and cytoplasmic thrombosthenin. Antibody staining of intact cells showed that membrane-associated thrombosthenin was localized, at least in part, in the exterior, "fluffy" coat of the platelet. Even after prolonged fixation and/or incubation with the various antisera, we were unable to demonstrate antibody penetration of intact, fixed platelets. Brief treatment with Pronase removed the surface-localized proteinaceous material and completely abolished all antibody staining.

Rafelson ME Jr, Booyse FM: Molecular aspects of platelet aggregation. In *Platelet Aggregation, ed. by J. Caen, Paris, Masson et Cie, 1971*

The development of a specific immunohistochemical technique has enabled us to localize the contractile protein, thrombosthenin both on the surface and in the cytoplasm of the human platelet. Specific antibody staining is used as a means of studying the conformational changes induced in the surface contractile protein of intact platelets after treatment with thrombin and ADP. The changes in surface-localized thrombosthenin appear to proceed in the following sequence:

1. Brief exposure to thrombin or adenosine diphosphate (ADP) produces unfolding and projection of surface-extended structures, immunohistochemically identifiable as thrombosthenin (or its moieties).

2. Longer exposure to thrombin or ADP produces extensive formation of distinct interplatelet bridges that are also immunohistochemically identifiable as thrombosthenin; these bridges appear to form over a maximum interplatelet distance of 1.500 to 2.00 Å.

3. Rapid shortening (contraction) and thickening of the interplatelet bridges takes place resulting in a complete blending of the external platelet surfaces.

We conclude from these data that conformational changes in the surface-localized thrombosthenin are very early events in the molecular mechanism of platelet aggregation and that thrombosthenin is directly involved in the formation of bridges between adjacent platelets. What we do not know, however, is whether the induced surface projections and the subsequent interplatelet bonds contain only thrombosthenin. It is possible that the projections and subsequent interplatelet bonds contain additional substances. It is also possible that these elements are composed of either the myosin or actin-like moieties of thrombosthenin. We are currently extending our studies with specific antisera against platelet myosin, platelet actin, platelet fibrinogen and platelet glycoproteins in an attempt to resolve some of these problems. Attempts are also being made to isolate the surface projections in order to carry out direct analyses.

We also continue to maintain our original biases, namely that our contractile protein model for platelet aggregation now has considerable evidence for its basic if not detailed correctness, and that one must study very early events on the platelet surface if the phenomenon of aggregation is to be elucidated. Once aggregation has occurred, it is too late!

Cardiology

Carleton RA: Change in left ventricular volume during angio-cardiography. *Amer J Cardiol 27:460-463, May 1971*

Seven selective left ventricular angiocardiograms that permitted measurement of end-diastolic volume for five consecutive cardiac cycles were analyzed.

Neither end-diastolic volume nor end-systolic volume changed significantly between the first and second cycles after ventricular opacification. A progressive increase in the major and minor ventricular semiaxes occurred beginning with the third opacified cycle. Correspondingly, the average end-diastolic volume and end-systolic volume increased by 6.9 ml and 3.4 ml, respectively, between the second and third cardiac cycles. Ventricular volumes progressively increased between the third and fifth cardiac cycles in each patient.

These data suggest that sodium diatrizoate has a negative inotropic effect on left ventricular myocardium by the third cardiac cycle after injection. Physiologic information from cineangiocardiography should be derived from the first two cardiac cycles after opacification.

Heller SJ, Carleton RA: Abnormal left ventricular contraction in patients with mitral stenosis. *Circulation 42:1099-1110, Dec 1970*

Twenty-five patients with pure mitral stenosis and nine normal subjects were studied by selective left ventricular cineangio-cardiography. Left ventricular volumes were measured at end systole, throughout diastole, and at end diastole. Although filling curves showed that the left ventricles filled slowly in patients with mitral stenosis, normal end-diastolic volumes were attained provided diastole lasted 400 msec. Despite normal end-diastolic volumes, end-systolic volumes were significantly larger ($P < 0.0005$) in the patients with mitral stenosis (av = 64.6 ml) than in normal subjects (30.8 ml). Correspondingly, left ventricular ejection fractions were significantly lower ($P < 0.0005$) in the patients with mitral stenosis (55.7 per cent) than in the normal subjects (76.7 per cent).

Qualitative analysis of the cineangiocardiograms demonstrated that 20 patients with mitral stenosis had distortion, immobility, and rigidity of the posterobasal area of the left ventricle.

It is hypothesized that a rigid "mitral complex" immobilizes the poserobasal area of the left ventricle in patients with mitral stenosis, thereby impairing left ventricular contraction, and that this impairment is an important factor in the reduced cardiac output of these patients.

Levin PD, Sessions RW, Passovoy M, Carleton RA: Patient and pacemaker surviva after pacemaker implantation. *Chest 58:4-7, July 1970*

One hundred thirty patients have had 244 pacemakers of five types implanted at Presbyterian-St. Luke's Hospital in the past eight years. There has been a 0.50 probability of successful unit function at only 12 months with epicardial units. All transvenous units used have had a 0.50 probability of unit success at more than 17 months. This fact, combined with the lower frequency of early death with transvenous units, has led to our opinion that epicardial units no longer have a place unless a thoracotomy is mandatory for other reasons. The data of the present study suggest an augmented early mortality with fixed-rate transvenous units compared with a unit which synchronizes with the intrinsic ventricular rhythm. This, with the comparable unit reliability, will lead us to use ventricular synchronous transvenous units increasingly in the future.

Gastroenterology

Apter JT, Hardison WGM: Parameter estimation in phospholipid regulation of bile salt stimulated cholesterol appearance in bile. *Proc Nat Electron Conf 26:2-6, 1970*

The relation between biliary bile salt excretion and biliary cholesterol and phospholipid excretion was studied in bile-fistula rats infused with graded doses of bile salt. With infusion of taurocholate, a micelle-forming bile salt, increase in biliary bile salt excretion was associated with an increase in biliary lipid excretion. With infusion of dehydrocholate, a non-micelle-forming bile salt, biliary lipid excretion increased little. With taurocholate infusion, the relation between biliary bile salt and lipid excretion was not linear. At high bile salt excretion rates, biliary lipid excretion rate increased little in spite of increasing biliary bile salt excretion rate. At very low bile salt and phospholipid excretion rates, cholesterol excretion remained disproportionately high. At low infusion rates, therefore, bile was more nearly saturated or supersaturated with cholesterol than at high rates. Micelle formation appears an important mechanism in biliary lipid excretion but it alone cannot explain the quantitative relation between biliary bile salt and lipid excretion.

Hedger RW, Hardison WGM: Transient macroamylasemia during an exacerbation of acute intermittent porphyria. *Gastroenterology 60:903-908, 1971*

The clinical course and laboratory data of a patient with acute intermittent porphyria and transient macroamylasemia are presented. Electrophoresis and gel filtration of the serum revealed the presence of normal amylase plus a large molecular complex (molecular weight greater than 100,000) with amylase activity. The macroamylase disappeared from the serum following remission of symptoms of acute intermittent porphyria. This is the first reported case of transient macroamylasemia. A method which might serve as a useful screening test for the presence of macroamylase is described.

Fried W, Johnson C, Heller P: Observations on regulation of erythropoiesis during prolonged periods of hypoxia. *Blood 36:607-616, 1970*

The experiments reported in this paper were designed to explain the phenomenon that plasma erythropoietin (Ep) levels reach peak titers after 8 hours of hypoxia and then fall to barely detectable levels after 72 hours. No single factor was found responsible for the decline of these levels with continued hypoxia, but both increase in the rate of erythropoiesis and increase in the hematrocrit contribute to this phenomenon. No decrease in the rate of clearance of injected erythropoietin was observed in hypoxic rats; therefore, it is likely that the production of Ep decreased.

The fall in the plasma Ep level with continued hypoxia is not associated with decrease in the rate of erythropoiesis, suggesting that the initiation of increased erythropoiesis requires higher Ep levels than its maintenance during continued hypoxia. The reason for this difference remains speculative.

Fried W, Knospe WH, Gregory SA, Trobaugh FE, Dansbie M, Conti SA: Factors regulating the proliferation and migration of hematopoietic stem cells. *J Lab Clin Med 77:239-246, 1971*

Hematopoietic stem cells (HSC) in the marrow, blood, and spleens of mice exposed to priming irradiation (300R with a leg shielded) seven days prior to exposure to 800R regenerated more rapidly than did the HSC in tissues of mice not given priming irradiation. HSC in marrow shielded during priming irradiation did not increase in number when the mice were given no further irradiation. However, after being exposed to 200R whole-body irradiation seven days after priming irradiation, they regenerated at a more rapid rate than did HSC in the marrow of mice unexposed to priming irradiation. HSC in the protected marrow of mice exposed to priming irradiation four days previously were no more sensitive to vinblastine than HSC in normal marrow. However, those in the marrow irradiated during priming x-radiation were significantly more sensitive to the damaging effects of vinblastine. We suggest the following hypothesis to explain these results. Irradiation damage releases a humoral substance which stimulates proliferation of surviving HSC. In nondepleted marrow spaces, cell-cell interaction prevents HSC from responding to this proliferative stimulus, whereas in irradiation-depleted marrow sites, this cell-cell interaction is overridden by the humoral stimulus to proliferation.

Friedel R, Mattenheimer H: On the origin of lactate dehydrogenase and other cell enzymes in normal blood serum. *Z Anal Chem 252:204-209, 1970*

The origin of cell enzymes in normal blood serum is as yet unexplained. In a comparative study in man, marmoset monkey, rat and mouse we have investigated which of 10 major organs could be excluded as significant sources of lactate dehydrogenase (LDH) in normal serum. LDH-1, LDH-2 and LDH-3 are the strongest isoenzyme fractions in serum of man and marmoset. Based on the LDH isoenzyme patterns liver and skeleton muscle were excluded in man; liver, skeleton muscle, spleen, large intestine and leucocytes were excluded in the marmoset. LDH-5 is the predominant isoenzyme in the serum of the rat and of the mouse. Heart and kidney were excluded as LDH sources in the rat; heart, kidney and lung were excluded in the mouse. One must assume that the mechanism of cell enzyme release into the blood is identical in all species. Hence, if an organ is excluded as source of LDH

in one species it is also to be excluded in all other species. Erythrocytes and thrombocytes were recognized as the sources of LDH in normal serum of the four species. Species differences of the LDH isoenzyme patterns in these organs are reflected in comparable differences of the isoenzyme patterns in serum. The major portion of LDH in normal serum is released during the physiological turnover of these cells. This hypothesis includes all enzymes which are present in erythrocytes and thrombocytes. Only few organ specific enzymes which are present in normal serum, originate from other tissues.

Friedel R, Mattenheimer H: Release of metabolic enzymes from platelets during blood clotting of man, dog, rabbit and rat. *Clin Chim Acta 30:37-46, 1970*

The release of metabolic enzymes from platelets during clotting of blood and the subsequent increase of enzyme activities in serum were studied in man, dog, rabbit and rat. The activities of enzymes were measured which are present in blood cells with high activity (lactate and malate dehydrogenases) and low activity (aspartate aminotransferase). Alanine aminotransferase was included because its activity in blood cells is at the limit of being detectable. Serum was prepared from native plasma and from blood at various times during clotting. The activities of lactate and malate dehydrogenases and of aspartate aminotransferase increased in serum with time during clotting; the increases in man were not large enough to be of significance in routine diagnostic enzymology. The magnitude of the activity increases in serum of the animals was such that enzyme measurements must be made either in plasma or in serum prepared from native plasma. Enzymes are mainly released from platelets and not from other formed elements in the blood. When platelet-rich plasma was allowed to clot, the increase of enzyme activities was similar to the increase observed during the clotting of blood. The pattern of enzyme activity increase in serum resembled closely the activity pattern in platelets.

Gregory SA, Fried W, Knospe WH, Trobaugh FE: Accelerated regeneration of transplanted hematopoietic stem cells in irradiated mice pretreated with cyclophosphamide. *Blood 37:196-203, 1971*

Results of experiments are reported which indicate that colony-forming units (CFU) regenerate more rapidly when transplanted into the marrow of lethally irradiated hosts pretreated with cyclophosphamide (CY) than when transplanted into those pretreated with saline. This effect is probably unrelated to the immunosuppressive properties of CY because it occurs in isogeneic strains as well as in randomly bred CF_1 mice. It also does not result from an increase in the radioresistance of cells which survive after injection of CY. The data presented here are compatible with the concept that CY somehow improves the environment for hematopoietic stem cell (HSC) proliferation and thereby causes an increased rate of regeneration of transplanted HSC in the marrow cavity of the host. The possibility that this is caused by release of HSC from an inhibitory effect of cell-cell interactions on proliferation or by the release of a humoral stimulus to HSC regeneration is discussed.

Knospe WH, Crosby WH: Aplastic anemia: A disorder of the bone-marrow sinusoidal microcirculation rather than stem-cell failure? *Lancet 20-22, Jan 1971*

Aplastic anemia may sometimes be caused by destruction of the sinusoidal microcirculation of the bone-marrow or "soil" rather than by hematopoietic stem-cell or "seed" failure. Experimentally such a lesion has followed large doses of localised x-irradiation in rats.

Aplastic disease of the marrow caused by a sinusoidal lesion cannot be repopulated by intravenously administered bone-marrow, but the marrow can be regenerated by bone-marrow curettage followed by local infusion of isogeneic marrow. Local infusion of bone-marrow may provide a vascular stem-cell which cannot be transplanted intravenously. A similar lesion of the sinusoidal microcirculation occurred in rats given lethal total body irradiation but protected with allogeneic bone-marrow. Late survivors developed a mild secondary syndrome with accompanying aplastic marrow and a defect of the sinusoidal microcirculation. The sinusoidal lesion may have been caused by immunological effects of a graft-versus-host reaction. Other experimental and clinical evidence is consistent with the hypothesis that aplastic disease of the marrow in human patients may result from immunological damage to the sinusoidal microcirculation. Such a hypothesis would explain the failure of isogeneic transplants to repopulate the marrow of patients with aplastic anemia. It would also explain the failure of endogenous stem-cell repopulation of aplastic marrow in patients with foci of active hematopoietic bone-marrow.

Knospe WH, Fried W, Gregory SA, Sasseti RJ, Trobaugh FE, Dansbie M, Conti SA: Effect of a noncellular spleen-derived factor on recovery of hematopoietic stem cells from irradiation. *J Lab Clin Med 76:584-592, 1970*

Implantation of irradiated mouse spleens into the peritoneal cavity of mice did not alter the number of hematopoietic stem cells in the femoral marrow when assayed by the spleen colony method. On the other hand, there was a significantly greater number of hematopoietic stem cells in femoral marrow of spleen-implanted mice as compared to those in saline-treated mice four days after exposure to 200r of x-radiation (given two hours after spleen implants). Injections of homogenates made from spleens and of a water-soluble fraction of this homogenate similarly resulted in an increase in the rate of hematopoietic stem cell regeneration following 200r. We postulate that a noncellular substance of splenic origin can increase stem cell proliferation in mice. Response to this stimulus is inhibited by the presence of a dense population of cells in the environment.

Knospe WH, Gregory SA: Smoldering acute leukemia. *Arch Intern Med 127:910-918, 1971*

Smoldering acute leukemia is a variant of acute granulocytic leukemia which may have a more benign course than the usual form of acute leukemia. The bone marrow shows increased numbers of blast cells and the blood shows cytopenias without blast cells. Such patients do not have life-threatening acute infection or bleeding seen in patients with acute leukemia. The absence of these findings help to distinguish smoldering acute leukemia from aleukemic leukemia. A study of six cases revealed elevated muramidase levels in three patients. Cytogenetic studies of marrow revealed diploid modes which may indicate a prolonged course. These patients should not receive aggressive chemotherapy which may accelerate the disease or precipitate complications. None of our patients received chemotherapy and survival ranged from six months to over two years.

Lange RD, McDonald TP, Jordan TA, Trobaugh FE, Kretchmar AL, Chernoff AI: The hemagglutination-inhibition assay for erythropoietin: A progress report. In *Hemopoietic Cellular Proliferation, edited by F Stohlman Jr, New York, Grune and Stratton, 1970, pp 122-132*

1. The hemagglutination-inhibition technic for the assay of erythropoietin has excellent reproducibility.

2. As little as 1.8 ± 0.1 milli-immunochemical units or erythropoietin can be detected with a precision of 8 per cent.

3. Erythropoietin was quantitatively recoverable when added to normal serum; on serial dilution, extracts of erythropoietin and erythropoietin-rich human serum demonstrated the same reaction slope.

4. Normal human serum has up to 60 milli-immunochemical ESF units per ml.

5. When related to hematocrit determinations, the hemagglutination-inhibition test showed reasonably good correlation; in patients with refractory and iron deficiency anemias, the ESF unitage determined biologically and immunochemically appeared to be positively correlated.

6. There was discordance between the biologic and immunochemical assays for ESF in the sera of patients with the anemia of uremia.

Infectious Diseases

Balagtas RC, Levin S, Nelson KE, Gotoff SP: Secondary and prolonged fevers in bacterial meningitis. *J Pediat 77:957-964, 1970*

The course of 88 patients with bacterial meningitis was reviewed to determine the incidence, etiology, and significance of secondary and prolonged fevers. Twenty-eight per cent developed secondary fever, and prolonged fever was noted in nine per cent. Phlebitis, drug fever, and unrelated infections were the major established causes of complicating fevers. Fever was not due to an inadequate response to antimicrobial therapy in this series. The differential diagnosis of fevers complicating the course of bacterial meningitis is emphasized to avoid improper management.

Nelson KE, Kallick CA, Levin S: Diphtheria in Chicago 1960-1970. *Illinois Med J 139:35, Jan 1971*

Diphtheria is still an important public health problem in Chicago. Analysis of the reported cases in Chicago between 1960 and November 30, 1970 indicated that most of the cases occurred among unimmunized or incompletely immunized children and adolescents. The frequency of infection was greatest among persons living on the North Side of the city, next on the West Side and least frequent on the South Side. The rates were highest in the Uptown Community area and they were similar in this area to that reported from the Southern states that have the highest incidence. The majority of the cases seen at the Municipal Contagious Disease Hospital had families from the Southern United States.

When clinical diphtheria occurs the consequence remains serious. The case fatality ratio in Chicago during the period of this study was 16.1%. This is slightly higher than the officially reported mortality rates in this country for the past four decades.

Carriers, when detected, often occurred among immunized children or adults. Asymptomatic carriers may have a significant role in the maintenance of andemic foci. When combined with an inadequately immunized group in the population, this could have led to a stable geographic focus in which repeated, apparently unrelated, outbreaks occurred.

It is essential for the control of diphtheria in Illinois that physicians first consider the diagnosis and then report all cases that are diagnosed so that an epidemiological investigation can be done.

The critical need, however, is for more complete protection of the population, especially those living in high risk areas, with diphtheria toxoid.

Bach GL, Pillay VKG, Kark RM: Immunoglobulin (IgA) deficiency in systemic lupus erythematosus. *Acta Rheum Scand 17:63-71, 1971*

A woman with an idiopathic convulsive disorder developed systemic lupus erythematosus while on a dilantin treatment. The patient's serum was IgA-deficient, a finding which prompted study of all available members of her family. Among 14 relatives, low to absent IgA levels were found five times suggesting a genetically determined pattern of IgA deficiency. Various clinical and laboratory data of the patient and her family are presented.

Frayser, R, Houston CS, Gray GW, Bryan AC, Rennie ID: The response of the retinal circulation to altitude. *Arch Intern Med 127:708-711, 1971*

The effect upon the retinal circulation of exposure to an altitude of 17,500 feet has been studied in acclimatized individuals and in those exposed for a short period. Retinal Blood flow is increased 89% over control values within two hours at altitude and is increased 128% after four days at altitude. It is increased 105% over control values in the acclimatized individuals. Retinal vessel size is maximal after four days at altitude and the vessels are smaller in the acclimatized subjects. All subjects are hypoxic and hypocapnic at 17,500 feet. These changes in the retinal circulation may reflect the changes which occur during acclimatization or a shift in the proportion of the neural tissue supplied by the retinal and choroidal circulations.

Gray GW, Bryan AC, Frayser R, Houston CS, Rennie IDB: Control of acute mountain sickness. *Aerospace Med 42:81-84, 1971*

Clinical trials of acetazolamide versus placebo and acetazolamide and furosemide were carried out at 17,500 feet (5400m), on Mount Logan. Subjects pretreated with acetazolamide before ascent were clinically well with minor symptoms of acute mountain sickness. Subjects started on fursemide on arrival at altitude quickly became medical casualties.

Acetazolamide is effective in ameliorating the symptoms of acute mountain sickness at very high altitude. It does not prevent pulmonary edema. Powerful diuretics such as furosemide do not protect against acute mountain sickness, and in fact may be dangerous at high altitude.

Hedger RW: The conservative management of acute oliguric renal failure. *Med Clin N Amer 55:121-135, 1971*

Acute oliguric renal failure is a catastrophic event and has a mortality of approximately 50 per cent. Mortality is directly related to age, type of causative injury, and the presence or absence of underlying renal disease. All these factors must be assessed in each case; then, with the use of a few basic principles and constant vigilance, optimum results can be obtained.

Because the mortality and morbidity are so high in acute oliguric renal failure, every effort should be made to prevent its occurrence. This can be done by insuring adequate hydration and blood volume before and after surgery; using the proper diuretics at the onset of oliguria in any clinical situation; and being constantly aware of renal involvement in the many disease entities that can produce renal failure.

Oyama JH: Diagnosis and treatment of lupus nephritis. *Med Clin N Amer 55:71-86, 1971*

There are some general principles that one can follow in the management of lupus nephritis.

First, the physician must have a high index of suspicion of renal involvement in any patient with systemic lupus erythematosus (SLE). The diagnosis of renal involvement should be confirmed with a renal biopsy for accurate assessment of the degree of involvement and a clearer prognosis.

When biopsy reveals no involvement, minimal involvement, or membranous changes only, therapy is directed toward control of clinical signs and symptoms. Urinalysis and simple tests of renal function should be repeated at intervals to detect any progression of renal involvement. The B_1C titer or whole complement activity should also be determined at intervals for evidence of disease activity.

In the instances in which initial biopsy reveals active lupus glomerulonephritis and in which renal function is well preserved (BUN less than 30 gm per 100 ml) high doses of prednisone (40 to 60 mg daily) for six months are recommended. During this interval, urinalysis, proteinuria, and renal function should be followed as parameters of improvement. At the end of the course of therapy, a renal biopsy should be assessed for histologic changes. If the renal lesion is still active and clinically the patient still demonstrates severe involvement, a course of nitrogen mustard treatment is recommended.

When initial evaluation and renal biopsy reveal severe involvement and compromised renal function, our present mode of treatment consists of high doses of steroids for four to six weeks, with close observation of urinalysis, proteinuria and renal function and B_1C titers for signs of improvement. If there appears to be little or no improvement, we recommend a course of nitrogen mustard followed by high doses of steroid. In many critically ill patients nitrogen mustard may be given at the outset.

In cases in which steroids or nitrogen mustards or both have not had a beneficial effect, we are presently investigating the efficacy of thiamphenicol (Thiocymetin). Our preliminary observations are that there has been good evidence of immunosuppression, but full evaluation of beneficial effects awaits further studies.

Rennie D, Lozano R, Monge C, Sime F, Whittembury J: Renal oxygenation in male Peruvian natives living permanently at high altitude. *J Appl Physiol 30:450-456, 1971*

Renal oxygenation was studied in six adult male volunteers of native Peruvian high-altitude stock. Two, who had each resided in Lima (160 m) for more than 10 years were studied in Lima and four, who had always resided in Cerro de Pasco (4,300 m) were studied in Cerro. In the four Cerro de Pasco participants C_{In} was normal (104 ml/min per 1.73 m^2) but a fall in C_{PAH} (391 ml/min per 1.73 m^2) associated with secondary polycythemia (hematocrit = 68%) raised filtration fraction to 27%. E_{PAH} was normal (92). Despite low Pa_{o2} (50.8 mm hg), true renal blood flow (1,320 ml/min per 1.73 m_2), arterial oxygen content (23.9 Vol. per cent) renal oxygen delivery 315 ml/min per 1.73 m^2), renal arteriovenous oxygen content gradients (1.19 vol%), and renal oxygen uptake (15.9 ml/min per 1.73 m^2) were all normal. The Po_2 gradient across the kidney was only 4.1 mm hg (compared with 29.5 mm Hg for the two Lima subjects in whom all results were normal). It is concluded that E_{PAH} is normal and that there is no evidence of deficient renal oxygenation in natives acclimatized to life at 4,300 m.

Obstetrics-Gynecology

Wolff JR, Nielson PE, Schiller PJ: Therapeutic abortion: Attitudes of medical personnel leading to complications in patient care. *Amer J Obstet Gynec 110:730-733, July 1971*

This study of the records of 50 consecutive patients undergoing a therapeutic abortion when compared with a control group reveals significant differences in attitudes of the staff that

affect patient care. Persistent themes are uneasiness and shame concerning personal participation, which led to avoidance by both attending staff and residents with a resultant inadequate experience. Information obtained from a series of seminars points to the conclusion that concern with the issue of causing a death remains paramount. Polarization and resolution of these feelings are fundamental and necessary if the demands of society for more abortions are to be met.

Virology

Deinhardt FW: Hepatitis. *Maryland Med J 20:59-62, Apr. 1971*

This paper summarizes the present status of hepatitis. With the intriguing demonstration of Australia antigen and the development of marmosets as experimental animal models, we can look for further advances in the near future.

Mohr JR, Holmes AW, Mattenheimer H, Deinhardt F, Schmidt FW: Enzymologic evaluation of experimental marmoset hepatitis. *Pol Arch Med Wewnet 44:549-554, 1970*

Marmosets, small new world monkeys, are easily infectable with virus hepatitis. Serum enzyme activities are usually more elevated during marmoset virus hepatitis than in that disease in man. Unlike in man high serum activity of glutamate dehydrogenase (GLDH) was found in marmosets, as well as elevation of some other serum enzyme activities, irrelevant in the diagnostics of human virus hepatitis. De Ritis index (GOT/GPT) was low, as in man.

Histologic examinations of the liver specimens taken by biopsy revealed signs of mild hepatitis.

Mohr JR, Mattenheimer H, Holmes AW, Deinhardt F, Schmidt FW: Experimental Hepatitis. *Enzyme 12:161-179, 1971*

Marmosets have been shown to develop hepatitis after inoculation of serum from patients with viral hepatitis. The activity alterations of lactate dehydrogenase, isocitrate dehydrogenase, alanine aminotransferase, aspartate aminotransferase, glutamate dehydrogenase, glucose-6-phosphate dehydrogenase, and phosphogluconate dehydrogenase in serum and liver tissue of marmosets with hepatitis suggest that these animals suffer from a mild but relatively protracted hepatocellular injury. Although the enzyme patterns are not identical to those seen in human viral hepatitis, they appear to resemble more closely the picture seen in that disease than in any other.

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